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(71) Applicant *(for all designated States except US)*: NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, CH–4058 Basel (CH).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: TRAXLER, Peter [CH/CH]; Bündtenring 3, CH–4124 Schönenbuch (CH). SEQUIN, Urs [CH/CH]; Hochfeldweg 25, CH–4106 Therwil (CH). GREEN, Jennifer, Mary [AU/CH]; Stallenmattstrasse 6, CH–4104 Oberwil (CH). FURET, Pascal [FR/FR]; 24, rue du Riegelsbourg, F–68800 Thann (FR).

(74) Agent: ROTH, Bernhard, M.; Novartis AG, Patent– und Markenabteilung, Lichtstrasse 35, CH–4002 Basel (CH).

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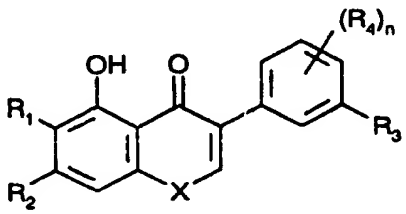

(I)

(57) Abstract

The invention relates to the use of a compound of formula (I), wherein R_1 and R_2, independently of each other, represent hydrogen, hydroxy or lower alkoxy, or R_1 and R_2 together form lower alkylenedioxy; R_3 is halogen, lower alkyl, halogen–substituted lower alkyl, hydroxy, phenyloxy, C_3–C_7–cycloalkyloxy or lower alkoxy; any R_4 is, independently of R_3 and independently of any other R_4 if present, selected from halogen, lower alkyl, halogen–substituted lower alkyl, hydroxy, phenyloxy, C_3–C_7–cycloalkyloxy or lower alkoxy; X is oxygen, imino or (halogen–substituted or unsubstituted lower alkanoyl, [lower alkyl or carboxy–, lower alkoxycarbonyl–, aminocarbonyl–, N–mono– or N,N–di–lower alkylamino carbonyl]–lower alkyl; or C_6–C_{12}–aryl)–substituted imino; and n is 0, 1, 3 or 4; or a salt thereof if at least one salt–forming group is present, in the treatment of certain diseases and the inhibition of protein kinases, as well as to new compounds of formula (I) and salts thereof.

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Phenyl-substituted bicyclic heterocyclyl derivatives and their use

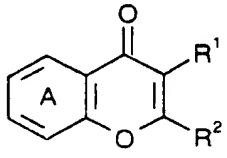
Summary of the Invention

The invention relates to the use of a phenyl-substituted bicyclic heterocyclyl derivative, or a salt thereof, in the inhibition of protein kinase activity, in the treatment of a proliferative disease that depends on protein kinase activity, especially of a tumour disease and/or of psoriasis if said disease is dependent on protein kinase activity; to its use in the preparation of a pharmaceutical composition for the treatment of said disease, to a pharmaceutical composition comprising said compound or a salt thereof, especially for the treatment of said disease, to a method of treatment of said disease with said compound or a salt thereof, to the use of said compound or a salt thereof for the inhibition of a protein tyrosine kinase, as well as to a novel phenyl-substituted bicyclic heterocyclyl derivative or a salt thereof, to such a novel compound or a salt thereof for use in a method for the diagnostic or therapeutic treatment of the human or animal body, to a process for its preparation, and/or to new intermediates or salts thereof.

Background of the Invention

Tumour diseases are one of the main causes of death in the industrial nations. Very great efforts are being made to make available effective ways and means of treating tumours. In particular, because of the large number and wide variety of possible tumour diseases, there is a constant need for new pharmaceutical compounds and compositions which, by virtue of their active ingredients, are suitable either for treating as many tumours as possible or, alternatively, for treating very specific tumours.

DE-OS 26 40 417 (published March 17, 1977) describes compounds of the formula



(II)

wherein

R^1 is an aryl group, a heteroaryl group, a cycloalkyl group, an aralkyl group, a lower alkoxy-group, an aryloxy group or an arylsulfonyl group;

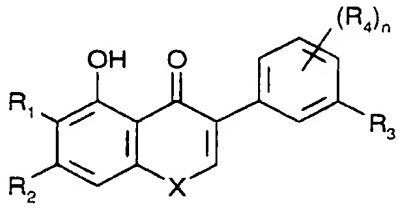
R^2 is hydrogen or lower alkyl; and

the ring A is unsubstituted or substituted by one or more halogen atoms or hydroxy, lower alkyl or lower alkoxy groups. These compounds are described to be effective as food additives that are capable of improving the growth of animals that are of economic importance or to improve the effectiveness of food metabolism in animals.

Surprisingly, it has now been found that the compounds of formula I show a totally different effect: While DE-OS 26 40 417 discloses the use of the compounds given above as food additives to increase growth e.g. in cattle, it has been found that isoflavonoids encompassed by the formula (II) given above as well as by the formula I given below, and the other compounds of formula I given below where X has one of the meanings different from oxygen, are tyrosine kinase inhibitors and, in full contrast to a growth increasing effect described in the prior art, show antiproliferative effects instead. Surprisingly, it has been found that the compounds mentioned hereinafter are suitable for the therapeutic treatment of protein kinase dependent tumour diseases and other protein kinase dependent proliferative diseases, such as psoriasis, as well as of other diseases which are described in greater detail below. Therefore, a totally new utility of the known compounds is part of the invention, as are new compounds.

Detailed description of the invention

In detail, a phenyl-substituted bicyclic heterocyclyl derivative that can be used in accordance with the invention is a compound of formula I,



(I)

wherein

R_1 and R_2, independently of each other, represent hydrogen, hydroxy or lower alkoxy, or R_1 and R_2 together form lower alkylenedioxy;

R_3 is halogen, lower alkyl, halogen substituted lower alkyl, hydroxy, phenyloxy, C_3-C_7-cycloalkyloxy or lower alkoxy;

any R_4 is, independently of R_3 and independently of any other R_4 if present, selected from halogen, lower alkyl, halogen substituted lower alkyl, hydroxy, phenyloxy, C_3-C_7-cycloalkyloxy or lower alkoxy;

X is oxygen, imino or (halogen-substituted or unsubstituted lower alkanoyl, [lower alkyl or carboxy-, lower alkoxycarbonyl-, aminocarbonyl-, N-mono- or N,N-di-lower alkylaminocarbonyl]-lower alkyl; or C_6-C_{12}-aryl)-substituted imino; and

n is 0, 1, 3 or 4;

or a salt thereof if at least one salt-forming group is present.

The above-mentioned use against protein kinase dependent tumours and other protein kinase dependent proliferative diseases, such as psoriasis, was not to be expected in any form. The same applies to the mode of action via protein kinase inhibition described below.

Accordingly, in a first general aspect the invention relates to the use of a compound of formula I, or a salt thereof, or a method of treatment of said compound or a salt thereof, for the therapeutic treatment of warm-blooded animals, especially humans, or to the use of said compound or a salt thereof in the preparation of pharmaceutical compositions for the treatment of a disease mentioned hereinbefore and hereinafter and/or, further, to a pharmaceutical composition comprising said compound or a salt thereof for use in the treatment of the diseases described hereinbefore and hereinafter.

Within the context of the present disclosure, the general terms used hereinbefore and hereinafter have preferably the following meanings, if not indicated otherwise:

The prefix "lower " used hereinbefore and hereinafter denotes a radical having up to and including a maximum of 7, especially up to and including a maximum of 4, and above all 1 or 2, carbon atoms.

"Further" or "furthermore" generally precedes radicals or definitions that are not as greatly preferred as those mentioned before them.

When asymmetric carbon atoms are present, the compounds of formulal may be in the form of mixtures of enantiomers or (where two or more centres of asymmetry are present) mixtures of diastereoisomers, or in the form of the pure enantiomers or diastereoisomers.

Lower alkoxy R_1 or R_2 is especially methoxy.

Lower alkylenedioxy formed together by R_1 and R_2 is preferably a bivalent radical selected from ethylenedioxy (-O-CH_2-CH_2-O-) and especially methylenedioxy (-O-CH_2-O-).

Halogen R_3 is fluorine, iodine or preferably bromine or chlorine. R_3 is preferably chlorine.

Lower alkyl R_3 is preferably methyl or ethyl.

Halogen substituted lower alkyl R_3 or R_4 is lower alkyl, such as methyl, that is substituted by halogen, such as fluoro or chloro, and is especially trifluoromethyl.

C_3-C_7-Cycloalkyloxy is preferably cyclohexyloxy, lower alkoxy (which, in the group consisting of phenyloxy, C_3-C_7-cycloalkyloxy and lower alkoxy, is preferred) is especially ethoxy or more especially methoxy.

Halogen R_4 is, independently, defined as halogen R_3.

Lower alkyl R_4 is preferably methyl.

X is oxygen (-O-), imino (-NH-) or substituted imino (with H replaced by a substituent).

If X is oxygen, then compounds of the formula I are preferably not radioactive.

In (halogen-substituted or unsubstituted lower alkanoyl, [lower alkyl or carboxy-, lower alkoxycarbonyl-, aminocarbonyl-, N-mono- or N,N-di-lower alkylaminocarbonyl]-lower alkyl; or C_6-C_{12}-aryl)-substituted imino X, the imino substitutent is especially lower alkanoyl that is substituted by halogen or especially unsubstituted lower alkanoyl; lower alkyl, especially methyl, ethyl, n-propyl or isopropyl; or substituted lower alkyl (preferably methyl or ethyl),

wherein the substituents (one or more, especially one substituent) are selected from carboxy, lower-alkoxycarbonyl, such as methoxy- or ethoxycarbonyl, aminocarbonyl, N-mono- or N,N-di-lower alkylaminocarbonyl, or C_6-C_{12}-aryl, especially phenyl.

The index n is preferably 0 or 1, most preferably 0.

Salts of compounds of formula I are especially acid addition salts with organic or inorganic acids, especially the pharmaceutically acceptable, non-toxic salts. Suitable inorganic acids are, for example, carbonic acid (preferably in the form of the carbonates or hydrogen carbonates); hydrohalic acids, such as hydrochloric acid; sulfuric acid; or phosphoric acid. Suitable organic acids are, for example, carboxylic, phosphonic, sulfonic or sulfamic acids, for example acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, 2-hydroxybutyric acid, gluconic acid, glucosemonocarboxylic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid, citric acid, glucaric acid, galactaric acid, amino acids, such as glutamic acid, aspartic acid, N-methylglycine, acetylaminoacetic acid, N-acetylasparagine or N-acetylcystine, pyruvic acid, acetoacetic acid, phosphoserine, 2- or 3-glycerophosphoric acid, glucose-6-phosphoric acid, glucose-1-phosphoric acid, fructose-1,6-bis-phosphoric acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, adamantanecarboxylic acid, benzoic acid, salicylic acid, 1- or 3-hydroxynaphthyl-2-carboxylic acid, 3,4,5-trimethoxybenzoic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, 4-aminosalicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid, nicotinic acid, isonicotinic acid, glucuronic acid, galacturonic acid, methane- or ethane-sulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalene-disulfonic acid, 2-, 3- or 4-methylbenzenesulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsulfuric acid, N-cyclohexylsulfamic acid, N-methyl-, N-ethyl- or N-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid. Compounds of formula I having at least one free carboxy group are capable of forming internal salts or metal or ammonium salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts, or ammonium salts with ammonia or suitable organic amines, such as tertiary monoamines, for example triethylamine or tri(2-hydroxyethyl)amine, or heterocyclic bases, for example N-ethyl-piperidine or N,N'-dimethyl-piperazine.

For isolation or purification purposes it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. Salts that are pharmaceutically acceptable are used therapeutically and those salts are therefore preferred.

In view of the close relationship between the novel compounds in free form and in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the novel compounds, hereinbefore and hereinafter any reference to the free compounds is to be understood as referring also to the corresponding salts, as appropriate and expedient, and furthermore to solvates, such as hydrates, that are formed e.g. by precipitation from water or other solvents, either of the salts and/or of the free compounds.

The compounds of formula I have valuable pharmacologically useful properties. In particular they exhibit specific inhibitory activities that are of pharmacological interest. They are effective especially as tyrosine protein kinase inhibitors and/or (furthermore) as inhibitors of serine/threonine protein kinases; they exhibit, for example, powerful inhibition of the tyrosine kinase activity of the receptor for epidermal growth factor (EGF) and of c-erbB2 kinase. Those receptor-specific enzyme activities play a key role in signal transmission in a large number of mammalian cells, including human cells, especially epithelial cells, cells of the immune system and cells of the central and peripheral nervous system. For example, in various cell types, EGF-induced activation of receptor-associated tyrosine protein kinase (EGF-R-TPK) is a prerequisite for cell division and hence for the proliferation of the cell population. An increase in the number of EGF-receptor-specific tyrosine kinase inhibitors thus inhibits the proliferation of the cells. The same applies analogously to the other protein kinases mentioned hereinbefore and hereinafter.

In addition to or instead of inhibiting EGF-receptor tyrosine protein kinase, the compounds of formula I also inhibit to varying extents other tyrosine protein kinases that are involved in signal transmission mediated by trophic factors, for example abl kinase, especially v-abl kinase, kinases from the family of the src kinases, especially c-src kinase, lck, fyn; other kinases of the EGF family, for example c-erbB2 kinase (HER-2), c-erbB3 kinase, c-erbB4 kinase; members of the family of the PDGF-receptor tyrosine protein kinases, for example PDGF-receptor kinase, CSF-1 receptor kinase, Kit-receptor kinase, VEGF-receptor kinase

(e.g. KDR and Flt-1) and FGF-receptor kinase; the receptor kinase of the insulin-like growth factor (IGF-1 kinase), and/or serine/threonine kinases, for example protein kinase C or cdc kinases, all of which play a part in growth regulation and transformation in mammalian cells, including human cells.

The inhibition of EGF-receptor-specific tyrosine protein kinase (EGF-R-TPK) can be demonstrated using known methods, for example using the recombinant intracellular domain of the EGF-receptor (EGF-R ICD; see, for example, E. McGlynn *et al.*, Europ. J. Biochem. 207, 265-275 (1992)). Compared with the control without inhibitor, the compounds of formula I inhibit the enzyme activity by 50 % (IC_{50}), for example in a concentration of from 0.001 up to 10 μM, especially from 0.005 to 5 μM.

The action of the compounds of formula I on EGF-stimulated cellular tyrosine phos-phorylation in the EGF-receptor can be determined in the human A431 epithelial carcinoma cell line by means of an ELISA which is described in U. Trinks *et al.*, J. Med. Chem. 37:7, 1015-1027 (1994). In that test (EGFR-ELISA) the compounds of formula I preferably exhibit an IC_{50} of approximately from 0.1 to 10 μM.

Stimulation of quiescent BALB/c3T3 cells with EGF rapidly induces the expression of c-fos mRNA. Pretreatment of the cells with a compound of formula I before the stimulation with EGF inhibits c-fos expression. That test procedure is likewise described in U. Trinks *et al.*, J. Med. Chem. 37:7, 1015-1027 (1994).

In the micromolar range too, the compounds of formula I exhibit, for example, inhibition of the cell growth of EGF-dependent cell lines, for example the epidermoid BALB/c mouse keratinocyte cell line (see Weissmann, B.A., and Aaronson, S.A., Cell 32, 599 (1983)) or the A431 cell line, which are recognised useful standard sources of EGF-dependent epithelial cells (see Carpenter, G., and Zendegni, J. Anal. Biochem. 153, 279-282 (1985)). In a known test method (see Meyer *et al.*, Int. J. Cancer 43, 851 (1989)), the inhibitory activity of the compounds of formula I is determined, briefly, as follows: BALB/MK cells (10 000/microtitre plate well) are transferred to 96-well microtitre plates. The test compounds (dissolved in DMSO) are added in a series of concentrations (dilution series) in such a manner that the final concentration of DMSO is not greater than 1 % (v/v). After the addition, the plates are

incubated for three days during which the control cultures without test compound are able to undergo at least three cell-division cycles. The growth of the MK cells is measured by means of methylene blue staining: after the incubation the cells are fixed with glutaraldehyde, washed with water and stained with 0.05 % methylene blue. After a washing step the stain is eluted with 3 % HCl and the optical density per well of the microtitre plate is measured using a Titertek Multiskan at 665 nm. IC_{50} values are determined by a computer-aided system using the formula:

$$IC_{50} = [(OD_{test} - OD_{start})/(OD_{control} - OD_{start})] \times 100.$$

The IC_{50} value in those experiments is given as that concentration of the test compound in question that results in a cell count that is 50 % lower than that obtained using the control without inhibitor. The compounds of formula I exhibit inhibitory activity in the micromolar range, preferably an IC_{50} of approximately from 0.1 to 50 μM.

The compounds of formula I exhibit inhibition of the growth of tumour cells also *in vivo*, as shown, for example, by the following test: The test is based on inhibition of the growth of the human epidermoid carcinoma A431 (ATCC No. CRL 1555; American Type Culture Collection, Rockville, Maryland, USA; see Santon, J.B., *et al.*, Cancer Research 46, 4701-4705 (1986) and Ozawa, S., *et al.*, Int. J. Cancer 40, 706-710 (1987)), which is transplanted into female BALB/c nude mice (Bomholtgard, Denmark). That carcinoma exhibits a growth that correlates with the extent of the expression of the EGF-receptor. In the experiment, tumours having a volume of approximately 1 cm^3 cultured *in vivo* are surgically removed from experimental animals under sterile conditions. The tumours are comminuted and suspended in 10 volumes (w/v) of phosphate-buffered saline. The suspension is injected s.c. (0.2 ml/mouse in phosphate-buffered saline) into the left flank of the animals. Alternatively, 1 x 10^6 cells from an *in vitro* culture in 0.2 ml of phosphate-buffered saline can be injected. Treatment with test compounds of formula I is started 5 or 7 days after the transplant, when the tumours have reached a diameter of 4-5 mm. The test compound in question is administered (in different doses for different animal groups) once a day for 15 successive days. The tumour growth is determined by measuring the tumour diameter along three axes that are perpendicular to each other. The tumour volumes are calculated using the

known formula p x L x $D^2/6$ (see Evans, B.D., *et al.*, Brit. J. Cancer 45, 466-8 (1982)). The results are given as treatment/control percentages (T/C x 100 = T/C %).

As well as or instead of inhibiting EGF-receptor tyrosine protein kinase, the compounds of formula I also inhibit other tyrosine protein kinases that are involved in signal transmission mediated by trophic factors, for example abl kinase, such as especially v-abl kinase, kinases from the family of the src kinases, such as especially c-src kinase and c-erbB2 kinase (HER-2), and serine/threonine kinases, for example protein kinase C, all of which are involved in growth regulation and transformation in mammalian cells, including human cells.

The above-mentioned inhibition of v-abl tyrosine kinase is determined by the methods of N. Lydon *et al.*, Oncogene Research 5, 161-173 (1990) and J. F. Geissler *et al.*, Cancer Research 52, 4492-4498 (1992). In those methods [Val^5]-angiotensin II and [γ -^{32}P]-ATP are used as substrates.

The inhibition of c-erbB2 tyrosine kinase (HER-2) can be determined, for example, analogously to the method used for EGF-R-TPK (see C. House *et al.*, Europ. J. Biochem. 140, 363-367 (1984)). The c-erbB2 kinase can be isolated, and its activity determined, by means of protocols known *per se*, for example in accordance with T. Akiyama *et al.*, Science 232, 1644 (1986).

The compounds of formula I which inhibit the tyrosine kinase activity of the receptor for the epidermal growth factor (EGF) or of the other tyrosine protein kinases mentioned are therefore useful, for example, in the treatment of (a) proliferative disease(s), especially of benign or malignant tumour disease(s) and of epidermal hyperproliferation, such as especially psoriasis, especially if said diseases depend on the activity of a protein tyrosine kinase, especially EGF-R kinase. They are capable of effecting tumour regression and of preventing the formation of tumour metastases and the growth of micrometastases. They can be used especially in the case of epidermal hyperproliferation (psoriasis), in the treatment of a neoplasia of epithelial character, e.g. mammary carcinomas, and in the treatment of a leukaemia.

The inhibition of proliferation, e.g. of tumour cells or epithelial cells in psoriasis, might also follow a different mechanism which is not yet known - however, the present data strongly suggest that inhibition of protein kinases is the underlying principle.

In a broader aspect of the invention, the compounds of formula I (especially the novel compounds) can be used also in the treatment of those disorders of the immune system in which several or, especially, individual tyrosine protein kinases and/or (furthermore) serine/threonine protein kinases are involved; those compounds of formula I can also be used in the treatment of those disorders of the central or peripheral nervous system in which signal transmission by several or, especially, a single tyrosine protein kinase(s) and/or (furthermore) serine/threonine protein kinase(s) is/are involved.

In general, the present invention relates also to the use of the compounds of formula I in the inhibition of the mentioned protein kinases, especially protein tyrosine kinases, most especially EGF-R kinase.

The compounds of formula I may also be used for diagnostic purposes; for example, proliferating cells, such as tumour cells, obtained from mammals, especially humans, which will also grow in cell culture may be tested in cell culture for their sensitivity to compounds of formula I, thus allowing better determination of possible methods of treatment.

The compounds according to the invention may be used either on their own or in combination with other pharmacologically active substances, for example together with inhibitors of the enzymes of polyamine synthesis, inhibitors of protein kinase C, inhibitors of other tyrosine kinases, cytokines, negative growth regulators, for example TGF-b or IFN-b, aromatase inhibitors, antioestrogens and/or cytostatics.

In the preferred subjects of the invention mentioned hereinafter, general definitions can be replaced by the more specific definitions given at the beginning, where appropriate and expedient.

Preferred is the use of a compound of formula I, or a salt thereof, preferably as defined below, for the inhibition of a protein tyrosine kinase, especially EGF-R tyrosine kinase, either in vivo or in vitro.

More preferred is the use of a compound of formula I, preferably as defined below, or a salt thereof if at least one salt-forming group is present, for the treatment or in the preparation of a pharmaceutical formulation for the treatment of a disease that depends on protein kinase activity, especially protein tyrosine kinase activity; or a pharmaceutical preparation, preferably for the treatment of a disease that depends on protein kinase activity, especially protein tyrosine kinase activity, comprising a compound of formula I, preferably as defined below, or a salt thereof if at least one salt-forming group is present, together with at least one pharmaceutically acceptable carrier; or a method of treatment of a disease that depends on protein kinase activity, especially protein tyrosine kinase activity, said method comprising administering to an animal in need thereof an amount of a compound of formula I, preferably as defined below, or a salt thereof if at least one salt-forming group is present, that is effective in the inhibition of protein tyrosine kinase activity; the disease that depends on protein kinase activity, especially protein tyrosine kinase activity, being preferably a disease depending on EGF-R tyrosine kinase activity.

Especially preferred is the use of a compound of formula I, preferably as defined below, or a salt thereof if at least one salt-forming group is present, for the treatment or in the preparation of a pharmaceutical formulation for the treatment of a tumour disease, especially a neoplasia of epithelial character or a leukaemia, and/or of psoriasis, where said disease(s) depend(s) on protein tyrosine kinase activity; or a pharmaceutical preparation, preferably for the treatment of a tumour disease, especially a neoplasia of epithelial character or a leukemia, and/or of psoriasis, where said disease(s) depend(s) on protein tyrosine kinase activity, comprising a compound of formula I, preferably as defined below, or a salt thereof if at least one salt-forming group is present, together with at least one pharmaceutically acceptable carrier; or a method of treatment of a tumour disease and/or of psoriasis, where said disease(s) depend(s) on protein tyrosine kinase activity, said method comprising administering to an animal in need thereof an amount of a compound of formula I, preferably as defined below, or a salt thereof if at least one salt-forming group is present, that is effective in the treatment of said disease; the disease that depends on protein tyrosine kinase activity being preferably a disease depending on EGF-R tyrosine kinase activity.

Preferred for the use(s), pharmaceutical composition(s), its (their) preparation and the method(s) of treatment mentioned above and below is a compound of the formula I, wherein
R_1 and R_2, independently of each other, represent hydrogen; hydroxy; or lower alkoxy, especially methoxy; or together form lower alkylenedioxy, especially methylenedioxy; preferably R_2 being selected from the group comprising hydroxy; and lower alkoxy, especially methoxy; and R_1 being selected from the group comprising hydrogen; and, independently of R_2, from hydroxy; or from lower alkoxy, especially methoxy;

R_3 is halogen, especially chlorine or bromine or hydroxy;

R_4 is, independently of R_3, halogen, especially chlorine, R_4 if present being fixed preferably in the 4-position of the phenyl ring in formula I;

X is oxygen, imino or imino substituted with lower alkanoyl, especially acetyl; lower alkyl, especially methyl, ethyl, n-propyl or isopropyl; carboxy-lower alkyl, such as carboxymethyl ($-CH_2-COOH$); lower-alkoxycarbonyl-lower alkyl, such as methoxycarbonylmethyl or ethoxycarbonylmethyl ($-CH_2-COOCH_3$ or $-CH_2-COOCH_2.CH_3$); aminocarbonyl ($-CO-NH_2$); or phenyl-lower alkyl, especially 2-phenylethyl;

and
n is 0 or 1,

or a salt thereof if at least one salt-forming group is present.

More preferred for the use(s), pharmaceutical composition(s), its (their) preparation and the method(s) of treatment mentioned above and below is a compound of the formula I, wherein
R_1 and R_2, independently of each other, represent hydrogen; hydroxy; or lower alkoxy, especially methoxy; or together form lower alkylenedioxy, especially methylenedioxy; preferably R_2 being selected from the group comprising hydroxy; and lower alkoxy, especially methoxy; and R_1 being selected from the group comprising hydrogen; and, independently of R_2, from hydroxy; or from lower alkoxy, especially methoxy;

R_3 is halogen, especially chlorine or bromine or hydroxy;

R_4 is, independently of R_3, halogen, especially chlorine, R_4 if present being fixed preferably in the 4-position of the phenyl ring in formula I;

X is oxygen, and

n is 0 or 1,

or a salt thereof if at least one salt-forming group is present.

Even more preferred for the use(s), pharmaceutical composition(s), its (their) preparation and the method(s) of treatment mentioned above and below is a compound of the formula I selected from the group comprising
3-(3-chlorophenyl)-5,7-dihydroxy-isoflavone;
3-(3-chorophenyl)-5-hydroxy-7-methoxy-isoflavone;
3-(3-bromophenyl)-5,7-dihydroxy-isoflavone;
3-(3-bromophenyl-5-hydroxy-7-methoxy-isoflavone;
3-(3-chlorophenyl)-5,6,7-trihydroxy-isoflavone;
3-(3-bromophenyl)-5,6,7-trihydroxy-isoflavone;
3-(3-chlorophenyl)-5,6-dihydroxy-7-methoxy-isoflavone;
3-(3-bromophenyl)-5,6-dihydroxy-7-methoxy-isoflavone;
3-(3-chlorophenyl)-5-hydroxy-6,7-dimethoxy-isoflavone;
3-(3-bromophenyl)-5-hydroxy-6,7-dimethoxy-isoflavone;
3-(3-chlorophenyl)-5-hydroxy-6,7-methylenedioxy-isoflavone;
3-(3-bromophenyl)-5-hydroxy-6,7-methylenedioxy-isoflavone;
3-(3,4-Dichlorophenyl)-5,7-dihydroxy-isoflavone; and
3-(3,4-Dichlorophenyl)-5-hydroxy-7-methoxy-isoflavone;
or a salt thereof, where salt-froming groups are present.

The invention also relates to novel compounds of the formula I, or salts thereof where salt-froming groups are present.

Of the novel compounds of formula I according to the invention as such, there is preferred a compound of the formula I, wherein
R_1 and R_2, independently of each other, represent hydrogen; hydroxy; or lower alkoxy, especially methoxy; or together form lower alkylenedioxy, especially methylenedioxy; preferably R_2 being selected from the group comprising hydroxy; and lower alkoxy, especially methoxy; and R_1 being selected from the group comprising hydrogen; and, independently of R_2, from hydroxy; or from lower alkoxy, especially methoxy;

R_3 is halogen, especially chlorine or bromine, or hydroxy;

R_4 is, independently of R_3, halogen, especially chlorine, R_4 if present being fixed preferably in the 4-position of the phenyl ring in formula I;

X is oxygen, imino or imino substituted with lower alkanoyl, especially acetyl; lower alkyl, especially methyl, ethyl, n-propyl or isopropyl; carboxy-lower alkyl, such as carboxymethyl ($-CH_2-COOH$); lower-alkoxycarbonyl-lower alkyl, such as methoxycarbonylmethyl or ethoxycarbonylmethyl ($-CH_2-COOCH_3$ or $-CH_2-COOCH_2.CH_3$); aminocarbonyl ($-CO-NH_2$); or phenyl-lower alkyl, especially 2-phenylethyl;

and
n is 0 or 1,

with the proviso that, (i) when X is oxygen and the other moieties are as defined above, then R_3 is halogen, and (ii) when X is oxygen and R_1 is hydrogen and the other moieties have the meanings given above, then R_2 is lower alkoxy, especially methoxy;

or a salt thereof if at least one salt-forming group is present.

More preferred is a compound as such of the formula I, wherein
R_1 and R_2, independently of each other, represent hydrogen; hydroxy; or lower alkoxy, especially methoxy; or together form lower alkylenedioxy, especially methylenedioxy; preferably R_2 being selected from the group comprising hydroxy; and lower alkoxy,

especially methoxy; and R_1 being selected from the group comprising hydrogen; and, independently of R_2, from hydroxy; or from lower alkoxy, especially methoxy;

R_3 is halogen, especially chlorine or bromine, or hydroxy;

R_4 is, independently of R_3, halogen, especially chlorine, R_4 if present being fixed preferably in the 4-position of the phenyl ring in formula I;

X is imino or imino substituted with lower alkanoyl, especially acetyl; lower alkyl, especially methyl, ethyl, n-propyl or isopropyl; carboxy-lower alkyl, such as carboxymethyl ($-CH_2-COOH$); lower-alkoxycarbonyl-lower alkyl, such as methoxycarbonylmethyl or ethoxycarbonylmethyl ($-CH_2-COOCH_3$ or $-CH_2-COOCH_2.CH_3$); aminocarbonyl ($-CO-NH_2$); or phenyl-lower alkyl, especially 2-phenylethyl;

and
n is 0 or 1,

or a salt thereof if at least one salt-forming group is present.

Most preferred is a compound as such of the formula I, wherein
R_1 and R_2, independently of each other, represent hydrogen; hydroxy; or lower alkoxy, especially methoxy; or together form lower alkylenedioxy, especially methylenedioxy; preferably R_2 being selected from the group comprising hydroxy; and lower alkoxy, especially methoxy; and R_1 being selected from the group comprising hydrogen; and, independently of R_2, from hydroxy; or from lower alkoxy, especially methoxy;

R_3 is halogen, especially chlorine or bromine or hydroxy;

R_4 is, independently of R_3, halogen, especially chlorine, R_4 if present being fixed preferably in the 4-position of the phenyl ring in formula I;

X is imino or imino substituted with lower alkyl, especially methyl, ethyl, n-propyl or isopropyl; lower-alkoxycarbonyl-lower alkyl, such as methoxycarbonylmethyl or ethoxycar-

bonylmethyl (-CH_2-$COOCH_3$ or -CH_2-$COOCH_2$.CH_3); or further aminocarbonyl (-CO-NH_2); or phenyl-lower alkyl, especially 2-phenylethyl;

and
n is 0 or 1, especially 0;

or a salt thereof if at least one salt-forming group is present.

Most preferred is any one of the following novel compounds of formula I as such, or a salt thereof where at least one salt-forming group is present:
3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone (very preferred);
3-(3-bromophenyl)-5-hydroxy-7-methoxy-4-quinolone;
3-(3,4-dichlorophenyl)-5-hydroxy-7-methoxy-4-quinolone;
3-(3-hydroxyphenyl)-5-hydroxy-7-methoxy-4-quinolone;
3-(3-chlorophenyl)-5-hydroxy-6,7-dimethoxy-4-quinolone;
3-(3-chlorophenyl)-5-hydroxy-6,7-methylenedioxy-4-quinolone;
3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone (very preferred);
3-(3-bromophenyl)-5,7-dihydroxy-4-quinolone;
3-(3,4-dichlorophenyl)-5,7-dihydroxy-4-quinolone;
3-(3-hydroxyphenyl)-5,7-dihydroxy-4-quinolone;
3-(3-chlorophenyl)-5,6,7-trihydroxy-4-quinolone;
N-methyl-3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone (very preferred);
N-(2-phenylethyl)-3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone (very preferred);
3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone-N-methylacetate (very preferred);
3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone-N-ethylacetate;
3-(3-chlorphenyl)-5-hydroxy-7-methoxy-4-quinolone-N-acetic acid;
3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone-N-acetamide;
N-acetyl-3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone;
N-ethyl-3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone;
N-propyl-3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone;
N-isopropyl-3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone;
3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone-N-acetic acid;
3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone-N-acetamide;

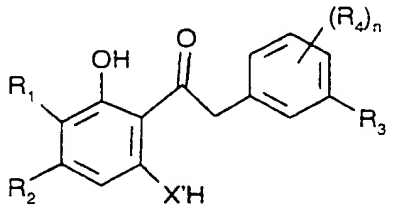
N-acetyl-3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone;
N-ethyl-3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone;
N-propyl-3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone; or
N-isopropyl-3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone.

Most preferred is also any one of the following novel compounds of formula I as such, or a salt thereof where at least one salt-forming group is present:
3-(3-chorophenyl)-5-hydroxy-7-methoxy-isoflavone (very preferred);
3-(3-bromophenyl)-5,7-dihydroxy-isoflavone;
3-(3-bromophenyl-5-hydroxy-7-methoxy-isoflavone;
3-(3-chlorophenyl)-5,6,7-trihydroxy-isoflavone;
3-(3-bromophenyl)-5,6,7-trihydroxy-isoflavone;
3-(3-chlorophenyl)-5,6-dihydroxy-7-methoxy-isoflavone;
3-(3-bromophenyl)-5,6-dihydroxy-7-methoxy-isoflavone;
3-(3-chlorophenyl)-5-hydroxy-6,7-dimethoxy-isoflavone;
3-(3-bromophenyl)-5-hydroxy-6,7-dimethoxy-isoflavone;
3-(3-chlorophenyl)-5-hydroxy-6,7-methylenedioxy-isoflavone;
3-(3-bromophenyl)-5-hydroxy-6,7-methylenedioxy-isoflavone;
3-(3,4-dichlorophenyl)-5,7-dihydroxy-isoflavone; or
3-(3,4-dichlorophenyl)-5-hydroxy-7-methoxy-isoflavone.

Also with regard to the novel compounds of formula I (or a salt thereof if at least one salt-forming group is present) mentioned above or below, the invention relates to the use thereof in the treatment of a disease that depends on protein kinase activity such as a tumour disease and/or of psoriasis, to its use in the preparation of a pharmaceutical composition for the treatment of said disease, to a pharmaceutical composition comprising said compound or a salt thereof, especially for the treatment of said disease, to a method of treatment of said disease with said compound or a salt thereof, to the use of said compound or a salt thereof for the inhibition of protein tyrosine kinase, as well as to such a novel compound or a salt thereof for use in a method for the diagnostic or therapeutic treatment of the human or animal body, to a process for its preparation, and/or to new intermediates or salts thereof.

The compounds of formula I can be prepared in accordance with methods that are known per se (processes based on novel intermediates and/or leading to novel compounds of formula I or salts thereof, especially the compounds mentioned to be novel in the present disclosure, being analogy processes that are novel at least by virtue of the fact that new starting materials are employed and/or that new compounds of formula I are the result), preferably by

reacting a phenylketone of the formula III,.



(III)

wherein R_1, R_2, R_3, R_4 and n have the meanings given above for compounds of formula I and wherein X' is oxygen (-O-) or imino (-NH-), any free functional groups present being protected if necessary by readily removable protecting groups,

with a reactive formaldehyde derivative, and removing any protecting groups that are present,

where a starting material where appropriate and where a salt forming group is present may also be used in the form of a salt;

and, if desired, transforming a compound of formula I into a different compond of formula I, converting a resulting free compound of formula I into a salt, converting a resulting salt of a compound of formula I into the free compound or into a different salt, and/or separating a mixture of isomeric compounds of formulal into the individual isomers.

Detailed description of the process steps

The above processes are described in detail below (see also German Offenlegungsschrift No.26 40 617 published March 17, 1977; J. Org. Chem., 404 (1923); J. Amer. Chem. Soc. 50, 145 (1928); Gazz. Chim. Ital. 79, 913 (1949); and Tetrahedron Lett. 14, 593-7 (1962), all of which are incorporated herewith by reference). In the more precise description that fol-

lows, unless otherwise indicated the radicals R_1, R_2, R_3, R_4 and X, as well as n, are as defined for compounds of formula I.

General points:
The end products of formula I may contain substituents that can also be used as protecting groups in starting materials for the preparation of other end products of formula I. Unless the context indicates otherwise, the term "protecting group" is used in this text to denote only a readily removable group that is not a constituent of the particular desired end product of formula I.

Protective groups for functional groups in starting materials (especially of formula III) whose reaction is to be avoided, in particular carboxyl, amino and hydroxyl groups, include, in particular, those protective groups (conventional protecting groups) which are customarily used in the synthesis of peptide compounds or else of cephalosporins and penicillins, and also nucleic acid derivatives and sugars. These protective groups can already be present in the precursors and are intended to protect the functional groups concerned against unwanted side reactions such as acylations, etherifications, esterifications, oxidations, solvolysis, etc. In certain cases, the protective groups can, in addition to this, have the effect of making the course of reactions selective, for example stereoselective. It is characteristic of protective groups that they are readily removable, i.e. without undesirable side reactions, for example solvolytically, reductively, photolytically or else enzymically, for example under physiological conditions as well, and that they are not present in the end products.

The protection of functional groups by such protective groups (introduction of protecting groups), the protective groups themselves, and also the reactions for eliminating them, are described, for example, in standard works such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in Th. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York 1981, in "The Peptides"; Volume 3 (E. Gross and J. Meienhofer, editors), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (Methods of Organic Chemistry), HoubenWeyl, 4th Edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jescheit, "Aminosäuren, Peptide, Proteine" (Amino Acids, Peptides and Proteins), Verlag Chemie, Weinheim, Deerfield Beach and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (Chemistry of the Carbohydrates:

Monosaccharides and Derivatives), Georg Thieme Verlag, Stuttgart 1974, all of which are herewith incorporated by reference.

The skilled person will know how to select protecting groups or combinations of protecting groups and methods for the introduction and removal of protecting groups or combinations of protecting groups that are useful in the desired reaction steps.

A carboxyl group is, for example, protected as an ester group which can be selectively cleaved under mild conditions. A carboxyl group which is protected in esterified form is primarily esterified with a lower alkyl group which is preferably branched in the 1 position of the lower alkyl group or is substituted by suitable substituents in the 1 or 2 position of the lower alkyl group. A protected carboxyl group which is esterified with a lower alkyl group is, for example, methoxycarbonyl or ethoxycarbonyl. A protected carboxyl group which is esterified with a lower alkyl group which is branched in the 1 position of the lower alkyl group is, for example, tert-lower-alkoxycarbonyl, for example tert-butoxycarbonyl. A protected carboxyl group which is esterified with a lower alkyl group which is substituted in the 1 or 2 position of the lower alkyl group by suitable substituents is, for example, 1-aryl-lower-alkoxycarbonyl, such as arylmethoxycarbonyl, having one or two aryl radicals, in which aryl is phenyl which is unsubstituted or is substituted once, twice or three times by, for example, lower alkyl, for example tert-lower-alkyl, such as tert-butyl, lower alkoxy, for example methoxy, hydroxyl, halogen, for example chlorine, and/or nitro, for example benzyloxycarbonyl, benzyloxycarbonyl which is substituted by the said substituents, for example 4-nitrobenzyloxycarbonyl or 4-methoxybenzyloxycarbonyl, diphenylmethoxycarbonyl or diphenylmethoxycarbonyl which is substituted by the said substituents, for example di-(4-methoxyphenyl)methoxycarbonyl, and, in addition, carboxyl which is esterified with a lower alkyl group, where the lower alkyl group is substituted in the 1 or 2 position by suitable substituents, such as 1-lower-alkoxy-lower-alkoxycarbonyl, for example methoxymethoxycarbonyl, 1-methoxyethoxycarbonyl or 1-ethoxyethoxycarbonyl, 1-lower-alkylthio-lower-alkoxycarbonyl, for example 1-methylthiomethoxycarbonyl or 1-ethylthioethoxycarbonyl, aroylmethoxycarbonyl, in which the aroyl group is benzoyl which is unsubstituted or substituted, for example, by halogen, such as bromine, for example phenacyloxycarbonyl, 2-halo-lower-alkoxycarbonyl, for example 2,2,2-trichloroethoxycarbonyl, 2-bromoethoxycarbonyl or 2-iodethoxycarbonyl, and also 2-(trisubstituted silyl)-lower-alkoxycarbonyl, in which the substituents, independently of each other, are in each case an aliphatic, araliphatic, cycloaliphatic or aromatic hydrocarbon radi-

cal which is unsubstituted or substituted, for example, by lower alkyl, lower alkoxy, aryl, halogen and/or nitro, for example lower alkyl which is unsubstituted or substituted as above, phenyl-lower alkyl, cycloalkyl or phenyl, for example 2-tri-lower-alkylsilyl-lower-alkoxycarbonyl, such as 2-tri-lower-alkylsilylethoxycarbonyl, for example 2-trimethylsilylethoxycarbonyl or 2-(di-n-butylmethylsilyl)ethoxycarbonyl, or 2-triarylsilylethoxycarbonyl, such as triphenylsilylethoxycarbonyl. A carboxyl group can also be protected as an organic silyloxycarbonyl group. An organic silyloxycarbonyl group is, for example, a tri-lower-alkylsilyloxycarbonyl group, for example trimethylsilyloxycarbonyl. The silicon atom of the silyloxycarbonyl group can also be substituted by two lower alkyl, for example methyl, groups, and an amino or carboxyl group of a second molecule of the formula I. Compounds possessing such protective groups can be prepared, for example, using corresponding tri-lower-alkylhalosilanes, such as tert-butyldimethylchlorosilane, as silylating agents. A carboxyl group can also be protected in the form of an internal ester with a hydroxyl group which is present in the molecule at a suitable distance, for example in the γ position with regard to the carboxyl group, i.e. in the form of a lactone, preferably a γ-lactone.

A protected carboxyl group is preferably tert-lower-alkoxycarbonyl, for example tert-butoxycarbonyl, benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 9-fluorenylmethoxycarbonyl or diphenylmethoxycarbonyl, or a protected carboxyl group in the form of a lactone, in particular a γ-lactone, and most preferably lower-alkoxycarbonyl, such as methoxycarbonyl or ethoxycarbonyl.

A protected amino group is protected by an amino protecting group, for example in the form of an acylamino, arylmethylamino, etherified mercaptoamino, 2-acyl-lower-alk-1-enylamino or silylamino group, or as an azido group. In an acylamino group, acyl is, for example, the acyl radical of an organic carboxylic acid having, for example, up to 18 carbon atoms, in particular of a lower-alkanecarboxylic acid which is unsubstituted or substituted, for example, by halogen or aryl, or of benzoic acid which is unsubstituted or substituted, for example, by halogen, lower alkoxy or nitro, or, preferably, of a carbonic acid semiester. Such acyl groups are, preferably, lower alkanoyl, such as acetyl, propionyl or pivaloyl, halo-lower-alkanoyl, for example 2-haloacetyl, such as 2-chloro-, 2-bromo-, 2-iodo-, 2,2,2-trifluoro- or 2,2,2-trichloroacetyl, benzoyl which is unsubstituted or substituted, for example, by halogen, lower alkoxy or nitro, such as benzoyl, 4-chlorobenzoyl, 4-methoxybenzoyl or 4-

nitrobenzoyl, lower-alkoxycarbonyl, lower-alkoxycarbonyl which is preferably branched in the 1 position of the lower-alkyl radical or is suitably substituted in the 1 or 2 position, for example tert-lower-alkoxycarbonyl, such as tert-butoxycarbonyl, 1-aryl-lower-alkoxycarbonyl, such as arylmethoxycarbonyl, having one, two or three aryl radicals which are phenyl which is unsubstituted or substituted once or more than once by, for example, lower alkyl, in particular tert-lower-alkyl, such as tert-butyl, lower alkoxy, such as methoxy, hydroxyl, halogen, such as chlorine, and/or nitro, for example benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, diphenylmethoxycarbonyl, 9-fluorenylmethoxycarbonyl or di-(4-methoxyphenyl)methoxycarbonyl, aroylmethoxycarbonyl, in which the aroyl group is benzoyl which is unsubstituted or preferably substituted, for example, by halogen, such as bromine, for example phenacyloxycarbonyl, 2-halo-lower-alkoxycarbonyl, for example 2,2,2-trichloroethoxycarbonyl, 2-bromoethoxycarbonyl or 2-iodoethoxycarbonyl, 2-(tri-substituted silyl)-lower-alkoxycarbonyl, for example 2-tri-lower-alkylsilyl-lower-alkoxycarbonyl such as 2-trimethylsilylethoxycarbonyl or 2-(di-n-butylmethylsilyl)ethoxycarbonyl, or triarylsilyl-lower-alkoxycarbonyl, for example 2-triphenylsilylethoxycarbonyl. In an arylmethylamino group, for example a mono-, di- or, in particular, tri-arylmethylamino group, the aryl radicals are, in particular, phenyl radicals which are unsubstituted or substituted. Examples of such groups are benzyl-, diphenylmethyl- or, in particular, trityl-amino. In an etherified mercaptoamino group, the mercapto group is primarily present as substituted arylthio or aryl-lower-alkylthio in which aryl is, for example, phenyl which is unsubstituted or substituted, for example, by lower alkyl, such as methyl or tert-butyl, lower alkoxy, such as methoxy, halogen, such as chlorine, and/or nitro, for example 4-nitrophenylthio. In a 2-acyl-lower-alk-1-enyl radical which can be used as an amino protective group, acyl is, for example, the corresponding radical of a lower-alkanecarboxylic acid, of a benzoic acid which is unsubstituted or substituted, for example, by lower alkyl, such as methyl or tert-butyl, lower alkoxy, such as methoxy, halogen, such as chlorine, and/or nitro, or, in particular, of a carbonic acid semiester, such as a carbonic acid lower-alkyl semiester. Corresponding protective groups are, primarily, 1-lower-alkanoyl-lower-alk-1-en-2-yl, for example 1-lower-alkanoyl-prop-1-en-2-yl, such as 1-acetyl-prop-1-en-2-yl, or lower-alkoxycarbonyl-lower-alk-1-en-2-yl, for example lower-alkoxycarbonyl-prop-1-en-2-yl, such as 1-ethoxycarbonyl-prop-1-en-2-yl. A silylamino group is, for example, a tri-lower-alkylsilylamino group, for example trimethylsilylamino or tert-butyldimethylsilylamino. The silicon atom of the silylamino group can also only be substituted by two lower alkyl groups, for example methyl groups, and the amino group or carboxyl group of a second molecule of the formula I. Compounds having such protective groups can be

prepared, for example, using the corresponding chlorosilanes, such as tert-butyldimethylchlorosilane, as silating agents. An amino group can also be protected by conversion into the protonated form; suitable corresponding anions are primarily those of strong inorganic acids, such as of sulfuric acid, phosphoric acid or hydrohalic acids, for example the chlorine or bromine anion, or of organic sulfonic acids, such as p-toluenesulfonic acid.

Preferred amino protective groups are lower-alkoxycarbonyl, phenyl-lower-alkoxycarbonyl, fluorenyl-lower-alkoxycarbonyl, 2-lower-alkanoyl-lower-alk-1-en-2-yl or lower-alkoxycarbonyl-lower-alk-1-en-2-yl, especially tert-butoxycarbonyl or benzyloxycarbonyl, or most preferably lower alkanoyl, especially acetyl.

A hydroxyl group can, for example, be protected by an acyl group, for example lower alkanoyl which is unsubstituted or substituted by halogen, such as chlorine, such as acetyl or 2,2-dichloroacetyl, or, in particular, by an acyl radical, which is specified for protected amino groups, of a carbonic acid semiester. A hydroxyl group can also be protected by tri-lower-alkylsilyl, for example trimethylsilyl, triisopropylsilyl or tert-butyldimethylsilyl, a readily detachable etherifying group, for example an alkyl group, such as tert-lower-alkyl, for example tert-butyl, an oxa- or a thia-aliphatic or -cycloaliphatic, in particular 2-oxa- or 2-thia-aliphatic or -cycloaliphatic, hydrocarbon radical, for example 1-lower-alkoxy-lower-alkyl or 1-lower-alkylthio-lower-alkyl, such as methoxymethyl, 1-methoxymethyl, 1-ethoxymethyl, methylthiomethyl, 1-methylthioethyl or 1-ethylthioethyl, or 2-oxa- or 2-thia-cycloalkyl having 5-7 ring atoms, such as 2-tetrahydrofuryl or 2-tetrahydropyranyl, or a corresponding thia analogue, and also by 1-phenyl-lower-alkyl, such as benzyl, diphenylmethyl or trityl, with it being possible for the phenyl radicals to be substituted, for example, by halogen, for example chlorine, lower alkoxy, for example methoxy, and/or nitro. More preferably, a hydroxyl group can be protected in the form of an C_6-C_{12}-aryl-lower alkyl or a lower alkyl ether, for example as lower-alkyl ether, especially as methyl ether, or as phenyl-lower alkyl ether, especially as benzyl ether. Two hydroxyl groups, in particular adjacent hydroxyl groups, which are present in a molecule, or an adjacent hydroxyl group and amino group, can, for example, be protected by bivalent protective groups, such as a methylene group which is preferably substituted, for example by one or two lower alkyl radicals or oxo, for example by unsubstituted or substituted alkylidene, for example lower alkylidene, such as isopropylidene, cycloalkylidene, such as cyclohexylidene, a carbonyl group or benzylidene. A hydroxyl group

which is located adjacent to a carboxyl group can be protected by the formation of an internal ester (lactone), in particular of a γ-lactone.

Preferably, a protected hydroxyl group is protected by lower alkyl, such as methyl.

Detachment of the protective groups which are not components of the desired end product of the formula I, for example the carboxyl, amino and/or hydroxy protective groups, is effected in a manner known per se, for example using solvolysis, in particular hydrolysis, alcoholysis or acidolysis, or by means of reduction, in particular hydrogenolysis, or by means of other reducing agents, and also photolysis, as desired stepwise or simultaneously, with it also being possible to use enzymatic methods. Detachment of the protective groups is described, for example, in the standard works which are mentioned above in the section on protective groups.

Thus, a protected carboxyl, for example, for example lower-alkoxycarbonyl (which is preferably branched in the 1 position), such as tert-lower-alkoxycarbonyl, lower-alkoxycarbonyl which is substituted in the 2 position by a tri-substituted silyl group or in the 1 position by lower alkoxy or lower-alkylthio, or diphenylmethoxycarbonyl which is unsubstituted or substituted, can be converted into free carboxyl by treatment with a suitable acid, such as formic acid, acetic acid, oxalix acid, hydrochloric acid or trifluoroacetic acid, if desired while adding a nucleophilic compound, such as phenol or anisole. Benzyloxycarbonyl which is unsubstituted or substituted can, for example, be set free by means of hydrogenolysis, i.e. by treatment with hydrogen in the presence of a metallic hydrogenation catalyst, such as a palladium catalyst. In addition, suitably substituted benzyloxycarbonyl, such as 4-nitrobenzyloxycarbonyl, can also be converted into free carboxyl by reduction, for example by treatment with an alkali metal dithionite, such as sodium dithionite, or with a reducing metal, for example zinc, or a reducing metal salt, such as a chromium(II) salt, for example chromium(II)chloride customarily in the presence of a hydrogen-releasing agent which, together with metal, can produce nascent hydrogen, such as an acid, primarily a suitable carboxylic acid, such as a lower-alkanecarboxylic acid which is unsubstituted or substituted, for example, by hydroxyl, for example acetic acid, formic acid, glycolic acid, diphenylglycolic acid, lactic acid, mandelic acid, 4-chloromandelic acid or tartaric acid, or an alcohol or thiol, with water preferably being added. By means of treating with a reducing metal or metal salt, as described above, 2-halo-lower-alkoxycarbonyl (if desired after converting a 2-bromo-lower-alkoxycar-

bonyl group into a corresponding 2-iodo-lower-alkoxycarbonyl group) or aroylmethoxycarbonyl can also be converted into free carboxyl. Aroylmethoxycarbonyl can be cleaved by treating with a nucleophilic, preferably salt-forming reagent, such as sodium thiophenoxide or sodium iodide. The carboxyl group can also be set free from 1-aryl-lower-alkoxycarbonyl, for example arylmethoxycarbonyl, such as benzyloxycarbonyl, by hydrolysing in the presence of a base such as an alkali metal hydroxide, for example sodium, lithium or potassium hydroxide. 2-(Tri-substituted silyl)-lower-alkoxycarbonyl, such as 2-tri-lower-alkylsilyl-lower-alkoxycarbonyl, can also be converted into free carboxyl by treating with a salt of hydrofluoric acid which provides the fluoride anion, such as an alkali metal fluoride, for example sodium or potassium fluoride, in the absence or presence of a macrocyclic polyether ("crown ether"), or with a fluoride of an organic quaternary base, such as tetra-lower-alkylammonium fluoride or tri-lower-alkylaryl-lower-alkylammonium fluoride, for example tetraethylammonium fluoride or tetrabutylammonium fluoride, in the presence of an aprotic, polar solvent, such as dimethyl sulfoxide, N,N-dimethylformamide or N,N-dimethylacetamide. Carboxyl which is protected as organic silyloxycarbonyl, such as tri-lower-alkylsilyloxycarbonyl, for example trimethylsilyloxycarbonyl, can be released solvolytically in a customary manner, for example by treating with water, an alcohol or acid, or, in addition, fluoride, as described above. Esterified carboxyl can also be set free enzymically, for example using esterases or suitable peptidases, for example esterified arginine or lysine, such as lysine methyl ester, using trypsin. Carboxyl which is protected as lower alkylester or as an internal ester, such as a g-lactone, can be released by hydrolysis in the presence of a hydroxide-containing base, such as an alkaline earth metal hydroxide or, in particular, an alkali metal hydroxide, for example NaOH, KOH or LiOH, in particular LiOH, with the corresponding protected hydroxyl group being set free simultaneously.

A protected amino group is set free in a manner which is known per se and which differs depending on the nature of the protective groups, preferably using solvolysis or reduction. Lower-alkoxycarbonylamino, such as tert-butoxycarbonylamino, can be cleaved in the presence of acids, for example mineral acids, for example hydrohalic acid, such as hydrochloric acid or hydrobromic acid, in particular hydrobromic acid, or of sulfuric acid or phosphoric acid, preferably of hydrochloric acid, or of relatively strong organic acids, such as formic acid, oxalic acid, trichloroacetic acid or trifluoroacetic acid, in polar solvents, for example water or a carboxylic acid, such as acetic acid or formic acid, esters, such as lower alkyl lower alkanoates, e.g. ethyl acetate, halohydrocarbons, such as chlorinated lower-alkanes,

for example dichloromethane or chloroform, or ethers, preferably cyclic ethers, such as dioxane, or in organic carboxylic acids which are liquid at the reaction temperature, without solvent, for example in formic acid. 2-Halo-lower-alkoxycarbonylamino (if desired, after converting a 2-bromo-lower-alkoxycarbonylamino group into a 2-iodo-lower-alkoxycarbonylamino group), aroylmethoxycarbonylamino or 4-nitrobenzyloxycarbonylamino can, for example, be cleaved by treating with a suitable reducing agent, such as zinc in the presence of a suitable carboxylic acid, such as aqueous acetic acid. Aroylmethoxycarbonylamino can also be cleaved by treating with a nucleophilic, preferably salt-forming, reagent such as sodium thiophenoxide, and 4-nitrobenzyloxycarbonylamino also by treating with an alkali metal dithionite, for example sodium dithionite. Substituted or unsubstituted diphenylmethoxycarbonylamino, tert-lower-alkoxycarbonylamino or 2-(trisubstituted silyl)-lower-alkoxycarbonylamino, such as 2-tri-lower-alkylsilyl-lower-alkoxycarbonylamino, can be cleaved by treating with a suitable acid, for example formic or trifluoroacetic acid, for example in a halogenated hydrocarbon, such as methylene chloride or chloroform (in particular, if hydroxyl which is simultaneously protected with benzyl is not to be set free), 1-aryl-lower-alkoxycarbonylamino, such as substituted or unsubstituted benzyloxycarbonylamino, can, for example, be cleaved by means of hydrogenolysis, i.e. by treating with hydrogen in the presence of a suitable hydrogenation catalyst, such as a palladium catalyst, for example bound to a support material, such as carbon, preferably in polar solvents, such as di-lower-alkyl-lower-alkanoylamides, for example dimethylformamide, ethers, such as cyclic ethers, for example dioxane, esters, such as lower-alkyl lower-alkanoates, for example ethyl acetate, or alcohols, such as methanol, ethanol or propanol, with methanol being particularly preferred, preferably, for example, at room temperature, substituted or unsubstituted triarylmethylamino or formylamino can be cleaved, for example, by treating with an acid, such as a mineral acid, for example hydrochloric acid, or an organic acid, for example formic, acetic or trifluoroacetic acid, if desired in the presence of water, and triphenylaminomethyl can be cleaved, in particular, by hydrogenolysis using a precious metal or precious metal oxide as catalyst, such as platinum, palladium or, in particular, palladium hydroxide, with the catalyst preferably being bonded to a support material, such as carbon, silica gel or aluminium oxide, in inert solvents, such as an ester, or preferably a lower-alkyl lower-alkanoate, such as ethyl acetate, at temperatures of from 20 to 80°C, in particular of from 50 to 70°C, if required under elevated pressure, for example between about 1 and 10 bar, and an amino group which is protected as silylamino can be set free, for example, by means of hydrolysis or alcoholysis. An amino group which is protected by 2-haloacetyl, for example 2-chloroacetyl, can be set free by

treating with thiourea in the presence of a base, or with a thiolate salt, such as an alkali metal thiolate of the thiourea, and subsequent solvolysis, such as alcoholysis or hydrolysis, of the resulting substitution product. An amino group which is protected by 2-(trisubstituted silyl)-lower-alkoxycarbonyl, such as 2-tri-lower-alkylsilyl-lower-alkoxycarbonyl, can also be converted into the free amino group by treating with a fluoride anion-providing salt of the hydrofluoric acid, as indicated above in connection with the release of a correspondingly protected carboxyl group. Silyl, such as trimethylsilyl or tert-butyldimethylsilyl, which is bonded directly to a heteroatom, such as nitrogen, can likewise be detached with fluoride ions, preferably using a fluoride of an organic, quaternary nitrogen base, such as tetra-lower-alkylammonium fluoride or tri-lower-alkylaryl-lower-alkylammonium fluoride, for example tetraethylammonium fluoride or tetrabutylammonium fluoride, in the presence of an aprotic, polar solvent, such as dimethyl sulfoxide or N,N-dimethylacetamide, or, in particular, of an ether, such as tetrahydrofuran, at temperatures between 0 and 50°C, in particular, for example, at room temperature.

Amino which is protected in the form of an azido group is converted into free amino, for example, by means of reduction for example by means of catalytic hydrogenation with hydrogen in the presence of a hydrogenation catalyst, such as platinum oxide, palladium or Raney nickel, by means of reduction with mercapto compounds, such as dithiothreitol or mercaptoethanol, or by treating with zinc in the presence of an acid, such as acetic acid. The catalytic hydrogenation is preferably carried out in an inert solvent, such as a halogenated hydrocarbon, for example methylene chloride, or else in water or a mixture of water and an organic solvent, such as an alcohol or dioxane, at from approximately 20°C to 25°C, or else while cooling or heating.

A hydroxyl group which is protected by a suitable acyl group, a tri-lower-alkylsilyl group or by substituted or unsubstituted 1-aryl(such as 1-phenyl)-lower-alkyl is set free in an analogous manner to a correspondingly protected amino group. A hydroxyl group which is protected by 2,2-dichloroacetyl is set free, for example, by basic hydrolysis, while a hydroxyl group which is protected by tert-lower-alkyl or by a 2-oxa- or 2-thia-aliphatic or -cycloaliphatic hydrocarbon radical is set free by acidolysis, for example by treating with a mineral acid or a strong carboxylic acid, for example trifluoroacetic acid. A hydroxyl group which is protected by benzyloxy is set free, for example, by means of hydrogenolysis, i.e. by treating with hydrogen in the presence of a suitable hydrogenation catalyst, such as a palladium

catalyst, for example bound to a support material, such as charcoal, preferably in polar solvents, such as di-lower-alkyl-lower-alkanoylamides, for example dimethylformamide, ethers, such as cyclic ethers, for example dioxane, esters, such as lower-alkylalkanoates, for example ethyl acetate, chlorinated hydrocarbons, such as dichloromethane, or alcohols, such as methanol, ethanol or propanol, with methanol being particularly preferred, or mixtures of two or more of these solvents, preferably, for example, at room temperature. Two hydroxyl groups, or an adjacent amino group and hydroxyl group, which are together protected by means of a bivalent protective group, preferably, for example, a methylene group which is substituted once or twice by lower alkyl, such as by lower alkylidene, for example isopropylidene, cycloalkylidene, for example cyclohexylidene, or benzylidene, can be set free by acidic solvolysis, particularly in the presence of a mineral acid or a strong organic acid. A tri-lower-alkylsilyl group is likewise detached by means of acidolysis, for example by mineral acid, preferably hydrofluoric acid, or a strong carboxylic acid. Hydroxyl can also preferably be set free from tri-lower-alkylsilyloxy by treating with a fluoride anion-providing salt of hydrofluoric acid, such as an alkali metal fluoride, for example sodium or potassium fluoride, in the absence or presence of a macrocyclic polyether ("crown ether"), or with a fluoride of an organic quaternary base, such as tetra-lower-alkylammonium fluoride or tri-lower-alkylaryl-lower-alkylammonium fluoride, for example tetraethylammonium fluoride or tetrabutylammonium fluoride, in the presence of an aprotic, polar solvent, such as dimethyl sulfoxide or N,N-dimethylacetamide. 2-Halo-lower-alkoxycarbonyl is removed by the above-mentioned reducing agents, for example reducing metal, such as zinc, reducing metal salts, such as chromium(II) salts, or by sulfur compounds, for example sodium dithionite or, preferably, sodium sulfide and carbon disulfide. Esterified hydroxyl groups, for example lower-alkanoyloxy, such as acetyloxy, can also be set free with esterases, while acylated amino can, for example, be set free using suitable peptidases. Etherified hydroxy, especially phenyl-lower alkoxy, such as benzyloxy, or lower alkoxy, such as methoxy, can preferably be cleaved in the presence of a boron trihalide, such as boron trichloride (at low temperatures, preferably in a halogenated hydrocarbon, especially methylene chloride, preferably in the temperature range from - 80 to 15 °C) or especially boron tribromide (in an inert solvent, such as a hydrocarbon, for example benzene, toluene of xylene, preferably in the temperature range from 20 °C to the boiling temperature of the reaction mixture), or with a phosphoryl trihalide, such as phosphoroxychloride (preferably in a N,N-di-lower alkylformamide, such as dimethyl formamide, at elevated temperatures, preferably in the range from 60 °C to the boiling temperature of the reaction mixture, for example at about 80 °C).

Especially in the case where for the reaction of the phenylketone of formula III said compound is present as an 2-hydroxy-6-loweralkoxy phenylketone (X' = O) or a 2-(acyl amino, especially 2-lower alkanoyl amino, such as 2-acetyl amino)-6-lower alkoxy phenylketone (X' = acylimino = -NH(acyl)-) and the reaction takes place with formamide in the presence of a phosphoryl trihalide, such as phosphoroxychloride ($POCl_3$), it is also possible to have simultaneous cleavage of the lower alkoxy group to a hydroxy group and/or the acylimino group to the respective free imino group X in the final product, especially if the reaction takes place at elevated temperatures, preferably in the range of from 40 °C to reflux temperature, for example from 70 °C to reflux temperature, that is cleavage of the mentioned protected group(s). If necessary, water is added after the reaction to obtain the desired compounds, e.g. by pouring the reaction mixture on ice or into ice water.

In the reaction of a phenylketone of the formula III with a reactive formaldehyde derivative, the reactive formaldehyde derivative is preferably a formylation reagent of the Vilsmeyer type, especially a N,N-di-lower alkylformamide, preferably dimethylformamide, or furthermore a formylation reagent of the Gattermann-Adams type (zinc cyanide in the presence of hydrogen chloride), formamide or formanilide (in the case of the two latter reagents in the presence of an inert gas, such as nitrogen). Preferred is a N,N-di-lower alkylformamide, especially N,N-dimethylformamide.

The reaction between the phenylketone of formula III and the reactive formaldehyde derivative, especially a N,N-di-lower alkyl formamide, preferably dimethylformamide, preferably takes place

(i) in the presence of a phosporyl trihalide, especially phosphoroxychloride ($POCl_3$), preferably in the absence of a further solvent and at temperatures ranging from 20 °C to the reflux temperature of the respective reactin mixture, especially between 70 °C and the reflux temperature, preferably first a complex between the N,N-di-lower alkyl formamide and the phosphoryl trihalide being allowed to form (preferably in a temperature range of from -20 to 20 °C), after which the phenylketone is added; and, where necessary, hydrolysis of the reaction mixture, e.g. by pouring it onto ice or into ice water;

(ii) in the presence of boron trifluoride etherate (the complex of boron trifluoride with diethyl ether) and a halide of a strong acid, either in an excess of the reactants (especially the N,N-di-lower alkyl formamide) or in inert organic solvents or solvent mixtures. The halide of a strong acid is preferably a chloride of a strong acid, phosporoxychloride, thionylchloride, phosgene, oxaloylchloride, lower alkane sulfonyl chloride, such as methane sulfonyl chloride, benzene sulfonylchloride or p-toluene sulfonylchloride being especially preferred. Especially preferred is the reaction with methane sulfonylchloride in the presence of boron trifluoride etherate. The reaction preferably takes place with a solution of a phenylketone of formula I which is dissolved in a solvent, the solvent preferably being dry formamide, to which solution the boron trifluoride etherate, preferably in an amount of 3 to 6 equivalents when related on the amount of the phenylketone, is added. To this solution then a further solution, which comprises the methane sulfonylchloride (preferably in an excess) in an excess of dry dimethylformamide is added, an excess of 1 equivalent of methane sulfonylchloride being added for each hydroxy group present in the phenylketone of formula III. The reaction preferably takes place at temperatures in the range from 40 °C up to the reflux temperature of the reaction mixture, for example at about 100 °C. The product is then obtained after addition of water to the reaction mixure or addition of the reaction mixture to water at lower temperatures, especially from about 0 °C to about 10 °C, for example by pouring the reaction mixture onto ice.

Process variant)ii) is especially preferred in the case where X' in the phenylketone of formula III is oxygen.

Both in reaction (i) and (ii) the formylation of the activated methylen group takes place in connection with ring closure that takes place practically simultaneously, so that (if required after removal of (a) protecting group(s) and/or working up) a compound of formula I is obtained directly.

Especially in the case where for the reaction of the phenylketone of formula III said compound is present as an 2-hydroxy-6-loweralkoxy phenylketone (X' = O) or a 2-(acyl amino, especially 2-lower alkanoyl amino, such as 2-acetyl amino)-6-lower alkoxy phenylketone (X' = acylimino = -NH(acyl)-) and the reaction takes place with formamide in the presence of a phosphoryl trihalide, such as phosphoroxychloride ($POCl_3$), it is also possible to have simultaneous cleavage of the lower alkoxy group to a hydroxy group and/or the acylimino group

to the respective free imino group X in the final product, especially if the reaction takes place at elevated temperatures, preferably in the range of from 40 °C to reflux temperature, for example from 70 °C to reflux temperature, that is cleavage of the mentioned protected group(s). If necessary, water is added after the reaction to obtain the desired compounds, e.g. by pouring the reaction mixture on ice or into ice water.

Additional process steps

The optional transformation (conversion) of a compound of formula I into a different compond of formula I takes place in principle under customary conditions.

Preferred among the reactions leading to such conversion is any of the following reactions, or a combination of twwo or more such reactions, where appropriate:

a) Conversion of hydroxy into etherified hydroxy (for example, hydroxy R_1, R_2, R_3 and/or R_4), e.g. lower alkoxy, especially methoxy: The reaction preferably takes place between a compound of formula I with at least one hydroxy group and a lower alkyl halogenide, such as methyl iodide, a lower alkane sulfate, such as dimethyl sulfate, in the presence of an alkali-metal salt of the respective alcohol of the formula I (obtainable, e.g., by use if potassium hydroxide in water) in water or preferably by reaction of a compound of formula I with at least one hydroxy group in a lower alkanol, such as ethanol or especially methanol, with diazomethane in etherial solution (can be obtained, e.g., from N-methyl-N-nitroso-toluene-sulfonamide, N-methylnitroso urea in the presence of diethylether and a strong base, such as potassium hydroxide) at a preferred temperature in the range from -40 to 20 °C, especially around -20 °C.

b) Ether cleavage of one or more etherified hydroxy, especially lower alkoxy (especially methoxy), group(s) (for example lower alkoxy R_1, R_2, R_3 and/or R_4) to the respective hydroxy group(s): The reaction is primarily taking place between a compound of formula I, wherein at least one etherified hydroxy group, such as methoxy, is present, and a boron trihalide, especially boron tribromide, preferably in an inert solvent, such as a hydrocarbon, especially benzene, toluene or xylene, or a mixture thereof, preferably at elevated temperature, such as between 60 and about 110 °C.

c) Introduction of substituents on imino X in order to obtain substituted amino X, especially acyl, lower alkyl or substituted lower alkyl: For introduction of an acyl substituent, the reaction is primarily taking place between an acid of the formula IV,

Y-H (IV)

wherein the residue Y is acyl, especially lower alkanoyl, such as acetyl, or a reactive derivative thereof, such as an acid halide, e.g. acetylchloride, or a symmetric anhydride, such as a lower alkanoyl anhydride, especially acetanhydride, if required in an appropriate solvent, such as an ehter, e.g. dioxane, in the presence of an acid binding base, such as a tertiary nitrogen base, e.g. pyridine, at preferred temperatures in the range from 0 °C to reflux temperature, preferably at 20 to 50 °C. For introduction of a lower alkyl or substituted lower alkyl substituent, the reaction is primarily taking place between a compound of the formula V

Z-Q (V)

wherein Z is lower alkyl or substituted lower alkyl and Q is a nucleofugal leaving group, preferably arylsulfonyl, such as p-toluolsulfonyl, alkylsulfonyl, such as methylsulfonyl, or halogen, such as chloro, bromo or iodo, in the presence of an acid binding compound, such as a carbonate or hydrogen carbonate salt, e.g. an alkalimetal carbonate or -hydrogen carbonate, especially potassium carbonate, in an appropriate solvent, e.g. an acid amide, such as N,N-dimethylformamide, at preferred temperatures ranging from 0 to 100 °C, especially from 20 to 30 °C.

d) Cleavage of ester bonds, e.g. of lower alkoxycarbonyl as a substituent in substituted imino X, to the respective free acid: The reaction primarily takes place under customary conditions fo the hydrolysis of esters, especially in the presence of hydroxide salts, such as alkaline metal hydroxides, especially lithium hydroxide or sodium hydroxide, at temperatures ranging from 0 °C to the reflux temperature of the reaction mixture, preferably from 20 °C to about 100 °C.

The conversion of a salt of a compound of formula I into a different salt is carried out, for example, in solvents, especially in organic solvents, more especially in polar organic solvents, very especially in esters, for example lower alkanoyl-lower alkyl esters, such as ethyl acetate, in amides, for example N,N-di-lower alkyl-lower alkanoylamides, such as dimethylformamide, in alcohols, for example hydroxy-lower alkanes, such as methanol, ethanol, ethylene glycol or glycerol, or aryl alcohols, such as phenols, for example phenol, or in dimethyl sulfoxide, in the absence or presence of water, preferably in the presence of water, or in water itself. Special preference is given to reaction in alcohols, such as the last-mentioned hydroxy-lower alkanes, in mixtures of such alcohols and water, or in water itself.

The reaction is carried out, for example, in free solution, but it may also be effected over chromatographic columns, for example by gel filtration. The reaction is carried out at temperatures from immediately above the freezing point to the boiling point of the solutions in question, preferably at from 0 to 50°C, especially at from 20 to 40°C, for example at room temperature, in the presence or absence of a protecting gas, such as nitrogen or argon.

The compounds of formula I and the salt-forming base or acid are used in suitable molar ratios, or the salt forming base or acid is employed in excess. Preferably, the individual components are used in the molar ratio that corresponds to the ratio of the molarity of the base of formulal and the acid in the resulting salts. The salts that are formed precipitate, for example, by themselves, in some cases only after cooling, or they are precipitated by the addition of solvents, especially of non-polar solvents, for example ethers, such as diethyl ether, or of water, and/or are obtained by partial or complete concentration by evaporation.

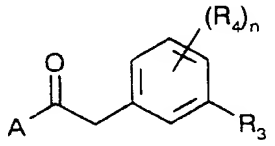
The reaction may also be effected via the free compounds of formula I, which are prepared, for example, by converting the base or acid salt of a base of formula I, with a first base or acid, used as starting material into the free compound with the aid of an acid or base, for example a hydroxy base, such as an alkali metal hydroxide, for example NaOH or KOH, or with an OH^--charged ion exchanger in aqueous solution in the presence or absence of an organic solvent, as defined above; the subsequent conversion of the free compound may be carried out, for example, as described above.

The free compounds of formula I are preferably prepared as just described, also by chromatography, for example by gel filtration, or over ion exchangers.

Mixtures of isomers obtainable according to the invention can be separated in a manner known per se into the individual isomers; diastereoisomers can be separated, for example, by partitioning between polyphasic solvent mixtures, recrystallisation and/or chromatographic separation, for example over silica gel, and racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the mixture of diastereoisomers so obtainable, for example by means of fractional crystallisation, or by chromatography over optically active column materials.

Starting materials:

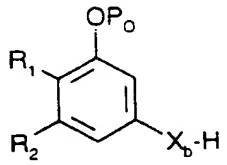
Starting materials of the formulae IV and V are known, commercially available and/or can be prepared according to known procedures. The same is true for the preparation of a compound of the III. Preferably, in the case that manufacture is necessary, a compound of the formula III is prepared by Friedel-Crafts reaction of an acid halogenide of the formula VI,



(VI)

wherein R_3, R_4 and n have the meanings given above for a compound of formula I and A is halogen, especially chloro or bromo, any free functional groups present being protected if necessary by readily removable protecting groups,

with a phenol deriative of the formula VII,



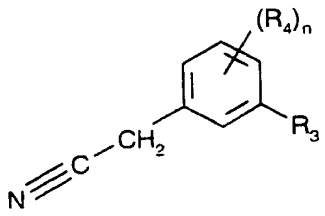
(VII)

wherein R_1 and R_2 are as defined for formula I, P_O is a hydroxy protecting group, preferably as mentioned above, especially methyl, and X_b is either oxygen or protected imino wherein the protecting group is one as described above for the protection of an amino group, especially lower alkanoyl, such as acetyl; any free functional groups present being protected if necessary by readily removable protecting groups,

the reaction taking place in the presence of a Friedel-Crafts-catalyst, especially stannic chloride ($SnCl_4$), in an appropriate solvent, e.g. a halogenated hydrocarbon, such as 1,2-dichloroethane, the reaction temperature preferably being in the range of from -20 to 50 °C, especially from 0 to 25 °C, and subsequent hydrolysis, especially with ice water. Where necessary, protecting groups can be removed after the reaction in accordance with the methods mentioned above for removal of protecting group to obtain a compound of formula I.

The starting materials of the formulae VI and VII are known, commercially available and/or can be prepared according to well-known procedures.

Alternatively, Houben-Hoesch reaction of a phenol derivative of formula VII, as mentioned above, wherein X_b preferably is oxygen, with a cyanide of the formula VIII,



(VIII)

wherein R_3, R_4 and n are as defined for a compound of formula I,
any free functional groups in a starting material of the formula VII and/or VIII present being protected if necessary by readily removable protecting groups, in the presence of an appropriate catalyst, such as aluminium chloride ($AlCl_3$) or preferably zinc chloride ($ZnCl_2$) and in an appropriate solvent, such as an ether, especially diethylether and subsequent hydrolysis in the presence of HCl (e.g. by pouring the reaction mixture on ice or into ice water). If necessary, protecting groups can be removed after the reaction in accordance with a method mentioned above for removal of protecting group to obtain a compound of formula I.

In particular, the starting materials can be prepared by methods analogous to those given in the examples.

General process conditions:
Free compounds of formula I having salt-forming properties that are obtainable in accordance with the process can be converted into their salts in a manner known per se, for example by treatment with acids or suitable derivatives thereof, or with bases, for example by the addition of the acid or base in question to the compound of formula I dissolved in a suitable solvent, for example an ether, such as a cyclic ether, especially dioxane or more especially tetrahydrofuran. Where appropriate and where a salt-forming group is present, starting materials and intermediates can also be used in the form of salts.

Mixtures of isomers obtainable according to the invention can be separated into the individual isomers in a manner known per se; racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the diastereoisomeric mixture so obtainable, for example by means of fractional crystallisation.

The reactions mentioned above can be carried out under reaction conditions that are known per se, in the absence or, customarily, in the presence of solvents or diluents, preferably solvents or diluents that are inert towards the reagents used and are solvents therefor, in the absence or presence of catalysts, condensation agents (e.g. phosphorus pentoxide) or neutralising agents, for example bases, especially nitrogen bases, such as triethylamine hydrochloride, depending on the nature of the reaction and/or of the reactants at reduced, normal or elevated temperature, for example in a temperature range of from approximately -80°C to approximately 200°C, preferably from approximately -20°C to approximately 150°C, for example at the boiling point of the solvent used, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under a nitrogen atmosphere.

Preference is given to the reaction conditions mentioned specifically in each case, especially the conditions or analogous conditions as mentioned in the examples.

Solvents and diluents are, for example, water, alcohols, for example lower alkyl hydroxides, such as methanol, ethanol, propanol or, especially, butanol, diols, such as ethylene glycol, triols, such as glycerol, or aryl alcohols, such as phenol, acid amides, for example carboxylic acid amides, such as dimethylformamide, dimethylacetamide or 1,3-dimethyl-3,4,5,6--tetrahydro-2(1H)-pyrimidinone (DMPU), carboxylic acids, especially formic acid or acetic acid, amides of inorganic acids, such as hexamethylphosphoric acid triamide, ethers, for example cyclic ethers, such as tetrahydrofuran or dioxane, or acyclic ethers, such as diethyl ether or ethylene glycol dimethyl ether, halogenated hydrocarbons, such as halo-lower alkanes, for example methylene chloride or chloroform, ketones, such as acetone, nitriles, such as acetonitrile, acid anhydrides, such as acetic anhydride, esters, such as ethyl acetate, bisalkanesulfines, such as dimethyl sulfoxide, nitrogen heterocycles, such as pyridine, hydrocarbons, for example lower alkanes, such as heptane, or aromatic compounds, such as benzene, toluene or xylene(s), or mixtures of those solvents, it being possible to select the solvents that are suitable for each of the above-mentioned reactions.

For working up the obtainable compounds of formula I or their salts there can be used customary processes, for example solvolysis of excess reagents; recrystallisation; chromatography, for example partition, ion or gel chromatography; partitioning between inorganic and organic solvent phases; extraction one or more times, especially after acidification or in-

creasing the basicity or the salt content; drying over hygroscopic salts; digestion; filtration; washing; dissolution; concentration by evaporation (if necessary in vacuo or under a high vacuum); distillation; crystallisation, for example of resulting compounds in oil form or from the mother liquor, inoculation with a crystal of the end product also being possible; or a combination of two or more of the mentioned working-up steps, which may also be used repeatedly.

Starting materials and intermediates may be used in pure form, for example after working up as mentioned above, in partially purified form or, for example, directly in the form of a crude product.

In view of the close relationship between the compounds of formula I in free form and in the form of salts, any reference hereinbefore and hereinafter to the free compounds or their salts is be understood as meaning also the corresponding salts or free compounds, respectively, where appropriate and expedient, provided that the compounds contain salt-forming groups. The compounds, including their salts, may also be obtained in the form of hydrates, or as solvates; their crystals may include, for example, the solvent used for crystallisation.

In the process of the present invention there are preferably used those starting materials which result in the novel compounds of formulal described at the beginning as being especially valuable.

The invention relates also to those forms of the process in which a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example a salt thereof.

Pharmaceutical compositions, the preparation thereof, and the use according to the invention of the compounds of formula I and compositions comprising those compounds as active ingredient

The present invention relates also to pharmaceutical compositions that comprise a compound of formula I, or a salt thereof, as active ingredient and that can be used especially in the treatment of the diseases mentioned at the beginning. Special preference is given to

compositions for enteral, such as nasal, buccal, rectal or, especially, oral, and parenteral, such as intravenous, intramuscular or subcutaneous, administration to warm-blooded animals, especially humans. The compositions comprise the active ingredient on its own or, preferably, together with a pharmaceutically acceptable carrier. The dose of active ingredient depends on the disease to be treated, and on the species, its age, weight and individual condition, on individual pharmacokinetic conditions, and on the mode of administration.

The invention relates also to pharmaceutical compositions for use in a method for the, especially therapeutic, treatment of the human or animal body, especially for the treatment of one of the diseases mentioned above, to a process for the preparation thereof (especially as compositions for the treatment of tumours and/or psoriasis), and to a method of treating a tumour disease and/or psoriasis , especially those diseases mentioned above.

The invention relates also to processes for, and to the use of compounds of formula I in, the preparation of pharmaceutical compositions that comprise compounds of formula I as active component (active ingredient).

Preference is given to a pharmaceutical composition that is suitable for administration to a warm-blooded animal, especially a human or furthermore a commercially usable mammal, suffering from a disease as described above, preferably from a disease that is responsive to inhibition of a protein kinase, especially a protein tyrosine kinase, preferably EGF-R kinase, for example psoriasis or a tumour, which composition comprises a compound of formula I, or a salt thereof where a salt-forming group is present, in an amount that is effective in the treatment o said disease, together with at least one pharmaceutically acceptable carrier.

Preference is given also to a pharmaceutical composition for the treatment of tumour diseases and/or psoriasis in a warm-blooded animal, especially a human or furthermore a commercially usable mammal, which requires such treatment, especially which is suffering from such a disease, which composition comprises as active ingredient a novel compound of formula I, or a pharmaceutically acceptable salt thereof, in an amount that is, especially, therapeutically effective against the mentioned disease.

The pharmaceutical compositions comprise from approximately 1% to approximately 95% active ingredient, dosage forms that are in single dose form preferably comprising from

approximately 20% to approximately 90% active ingredient, and dosage forms that are not in single dose form preferably comprising from approximately 5% to approximately 20% active ingredient. Unit dose forms are, for example, dragées, tablets, ampoules, vials, suppositories or capsules. Other dosage forms are, for example, ointments, creams, pastes, foams, tinctures, lipsticks, drops, sprays, dispersions, etc.. Examples are capsules comprising from approximately 0.05g to approximately 1.0g of the active ingredient.

The pharmaceutical compositions of the present invention are prepared in a manner known per se, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes.

There are preferably used solutions of the active ingredient, or suspensions or dispersions, especially isotonic aqueous solutions, dispersions or suspensions, which, for example in the case of lyophilised compositions comprising the active ingredient on its own or together with a carrier, e.g. mannitol, may be prepared before use. The pharmaceutical compositions may be sterilised and/or may comprise excipients, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers, and are prepared in a manner known per se, for example by means of conventional dissolving or lyophilising processes. Said solutions or suspensions may comprise viscosity--increasing substances, such as sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone or gelatin, and/or solubilisers, for example ®Tween 80 [polyoxyethylene(20) sorbitan monooleate; trade mark of ICI Americas, Inc, USA].

Suspensions in oil comprise as the oil component a vegetable, synthetic or semi-synthetic oils customarily used for injection purposes. There may be mentioned especially liquid fatty acid esters which contain as acid component a long-chain fatty acid having from 8 to 22, especially from 12 to 22, carbon atoms, for example lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, arachidic acid, behenic acid or corresponding unsaturated acids, for example oleic acid, elaidic acid, erucic acid, brassidic acid or linoleic acid, where appropriate with the addition of antioxidants, for example vitamin E, β-carotene or 3,5-di-tert-butyl-4-hydroxytoluene. The alcohol component of those fatty acid esters has not more than 6 carbon atoms and is a mono- or poly-valent, for example mono-, di- or tri-valent, alcohol, for example methanol, ethanol, propanol, butanol or

pentanol or their isomers, but especially glycol and glycerol. Accordingly, there may be mentioned as examples of fatty acid esters: ethyl oleate, isopropyl myristate, isopropyl palmitate, "Labrafil M2375" (polyoxyethylene glycerol trioleate from Gattefossé, Paris), "Labrafil M1944 CS" (unsaturated polyglycolised glycerides prepared by alcoholysis of apricot kernel oil and composed of glycerides and polyethylene glycol esters; Gattefossé, France); "Labrasol" (saturated polyglycolised glycerides prepared by alcoholysis of TCM and composed of glycerides and polyethylene glycol esters; Gattefossé, France) and/or "Miglyol 812" (triglyceride of saturated fatty acids having a chain length of from C_8 to C_{12} from Hüls AG, Germany), but especially vegetable oils, such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil and, more especially, peanut oil.

The preparation of the injection compositions is carried out in customary manner under sterile conditions, as are the introduction, for example, into ampoules or vials and the sealing of the containers.

Pharmaceutical compositions for oral administration can be obtained, for example, by combining the active ingredient with one or more solid carriers, granulating a resulting mixture, where appropriate, and processing the mixture or granules, if desired, where appropriate with the addition of additional excipients, to form tablets or dragée cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches and also carboxymethyl starch, cross-linked polyvinylpyrrolidone, or alginic acid or a salt thereof, such as sodium alginate. Additional excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol, or derivatives thereof.

Dragée cores can be provided with suitable, where appropriate enteric coatings, there being used inter alia concentrated sugar solutions, which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable

organic solvents or solvent mixtures or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colourings or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Pharmaceutical compositions for oral administration are also hard gelatin capsules, and soft sealed capsules consisting of gelatin and a plasticiser, such as glycerol or sorbitol. The hard gelatin capsules may comprise the active ingredient in the form of granules, for example in admixture with fillers, such as corn starch, binders and/or glidants, such as talc or magnesium stearate, and, where appropriate, stabilisers. In soft capsules the active ingredient is preferably dissolved or suspended in suitable liquid excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols or fatty acid esters of ethylene glycol or propylene glycol, it likewise being possible to add stabilisers and detergents, for example of the polyoxyethylene sorbitan fatty acid ester type.

Other oral dosage forms are, for example, syrups prepared in customary manner which comprise the active ingredient, for example, in suspended form and in a concentration of approximately from 5% to 20%, preferably approximately 10% or in a similar concentration that provides a suitable single dose when administered, for example, in a measure of 5 or 10 ml. Also suitable are, for example, powdered or liquid concentrates for the preparation of shakes, for example in milk. Such concentrates may also be packed in single dose quantities.

Suitable rectally administrable pharmaceutical compositions are, for example, suppositories that consist of a combination of the active ingredient with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols.

For parenteral administration there are suitable, especially, aqueous solutions of an active ingredient in water-soluble form, for example in the form of a water-soluble salt, or aqueous injection suspensions that comprise viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, if desired, stabilisers. The active ingredient, where appropriate together with one or more excipients, can also be in the form of a

lyophilisate and be made into a solution prior to parenteral administration by the addition of suitable solvents.

Solutions used, for example, for parenteral administration can also be used as infusion solutions.

Preferred preservatives are, for example, antioxidants, such as ascorbic acid, or microbicides, such as sorbic acid or benzoic acid.

Ointments are oil-in-water emulsions that comprise up to 70%, but preferably from 20 to 50%, water or aqueous phase. There are suitable as the fatty phase especially hydrocarbons, for example ®Vaseline, paraffin oil or hard paraffins, which, in order to improve the water-binding capacity, preferably contain suitable hydroxy compounds, such as fatty alcohols or esters thereof, for example cetyl alcohol or wool wax alcohols, such as wool wax. Emulsifiers are corresponding lipophilic substances, such as sorbitan fatty acid esters (®Spans), for example sorbitan oleate and/or sorbitan isostearate. Additives to the aqueous phase are, for example, humectants, such as polyalcohols, for example glycerol, propylene glycol, sorbitol and/or polyethylene glycol, or preservatives and perfumes.

Fatty ointments are anhydrous and comprise as base especially hydrocarbons, for example paraffin, Vaseline/ or paraffin oil, also natural or partially synthetic fats, for example coconut fatty acid triglyceride, or preferably hardened oils, for example hydrogenated peanut oil or castor oil, also fatty acid partial esters of glycerol, for example glycerol mono- and/or di-stearate, and also, for example, the fatty alcohols increasing water absorption, emulsifiers and/or additives mentioned in connection with the ointments.

Creams are oil-in-water emulsions that comprise more than 50% water. As oily base there are used especially fatty alcohols, for example lauryl, cetyl or stearyl alcohol, fatty acids, for example palmitic or stearic acid, liquid to solid waxes, for example isopropyl myristate, wool wax or beeswax, and/or hydrocarbons, for example ®Vaseline (petrolatum) or paraffin oil. Suitable emulsifiers are surface-active substances having predominantly hydrophilic properties, such as corresponding non-ionic emulsifiers, for example fatty acid esters of polyalcohols or ethylene oxide adducts thereof, such as polyglyceric acid fatty acid esters or

polyethylene sorbitan fatty acid esters (®Tween), and also polyoxyethylene fatty alcohol ethers or fatty acid esters, or corresponding ionic emulsifiers, such as alkali metal salts of fatty alcohol sulfates, for example sodium lauryl sulfate, sodium cetyl sulfate or sodium stearyl sulfate, which are usually used in the presence of fatty alcohols, for example cetyl alcohol or stearyl alcohol. Additives to the aqueous phase are inter alia agents that reduce the drying out of the creams, for example polyalcohols, such as glycerol, sorbitol, propylene glycol and/or polyethylene glycols, also preservatives and perfumes.

Pastes are creams and ointments having secretion-absorbing powder constituents, such as metal oxides, for example titanium oxide or zinc oxide, also talc and/or aluminium silicates, the purpose of which is to bind any moisture or secretions present.

Foams are administered from pressurised containers and are liquid oil-in-water emulsions in aerosol form, there being used as propellants halogenated hydrocarbons, such as chlorofluoro-lower alkanes, for example dichlorodifluoromethane and dichlorotetrafluoroethane, or preferably non-halogenated gaseous hydrocarbons, air, N_2O or carbon dioxide. As oil phase there are used inter alia the oil phases used above under ointments and creams, likewise the additives mentioned therein.

Tinctures and solutions generally have an aqueous-ethanolic base to which there are added inter alia polyalcohols, for example glycerol, glycols and/or polyethylene glycol, as humectants for reducing evaporation, and fat-restoring substances, such as fatty acid esters with low molecular weight polyethylene glycols, that is to say lipophilic substances that are soluble in the aqueous mixture, as a replacement for the fatty substances removed from the skin by the ethanol, and, if necessary, other excipients and additives.

The invention relates also to a process or a method for the treatment of the pathological conditions mentioned above, especially those which are responsive to inhibition of protein kinases. The compounds of formulal may be administered prophylactically or therapeutically as such or in the form of pharmaceutical compositions, preferably in an amount that is effective against the mentioned diseases, to a warm-blooded animal, for example a human, requiring such treatment, the compounds being used especially in the form of pharmaceutical compositions. In the case of a body weight of approximately 70kg, a daily dose of from

approximately 0.1g to approximately 5g, preferably from approximately 0.5g to approximately 2g, of a compound of the present invention is administered.

Examples

The following examples shall illustrate the present invention without being intended to limit the scope of the invention in any way. Abbreviations used are:

Anal.	Elementary Analysis
DMF	N,N-dimethylformamide
D_6-DMSO	perdeutero dimethyl sulfoxide
ether	diethyl ether
h	hour(s)
min	minute(s)
m.p.	melting point
MS	mass spectroscopy
^{1}H-NMR	proton nuclear magnetic resonance

Abbreviations used in data for NMR spectra

b	broad
d	doublet
J	coupling constant
m	multiplet
q	quartet
s	singlet
t	triplet

Example 1: 3-(3-Chlorophenyl)-5,7-dihydroxy-isoflavone

5.06 g (18.16 mMol) of 2-(3-chlorophenyl)-1-(2,4,6-trihydroxyphenyl)ethanone) is dissolved in 40 ml of DMF, and 14 ml (109 mMol) of boron trifluoride etherate is carefully added. 4.5 ml (54.5 mMol) of methanesulfonylchloride, dissolved in 40 ml of DMF, is added to the ketone-etherate mixture. The red solution is heated at 100 °C for 2 h, then poured onto ice, forming a yellowish mixture which gives a creamy precipitate after a few hours. The precipitate is collected by filtration, dissolved in ethyl acetate and washed with water. The organic phase is dried over sodium sulfate and evaporated to dryness yielding a red oil which is pu-

rified by flash chromatography using toluene/ethyl acetate 6:4 as eluent. 3-(3-Chlorophenyl)-5,7-dihydroxy-isoflavone is obtained which after crystallization from ethanol-water gives fine creamy needles of mp. 182.4-184.5 °C. ^{1}H-NMR (D_6-DMSO): 12.76 (s), 10.95 (s), 8.49 (s), 7.67 (s), 7.57-7.46 (m), 6.25 (d), 2.01; MS: m/z = 288 (M^+); Anal. ($C_{15}H_9O_4Cl$ (288.68): C 62.41 (found: 62.72), H 3.14 (found 3.46).

The starting material is prepared in the following way:

Step 1a) 2-(3-Chlorophenyl)-1-(2,4,6-trihydroxyphenyl)ethanone)

9.2 g (72.9 mMol) of phloroglucine (1,3,5-trihydroybenzene; Fluka, Buchs, Switzerland) and 11.05 g (72.9 mMol) of 3-chlorobenzylcyanide (Fluka, Buchs, Switzerland) are dissolved in 70 ml of anhydrous ether. Zinc chloride is added and a stream of dry hydrogen chloride is bubbled through the reaction mixture for 4 h. A viscous yellowish mass separates from the slightly brown solution. The flask is left closed overnight, and then the etheral layer is removed by decantation. 150 ml of 2 M HCl is added and the partly dissolved mass heated to 100 °C for 2.5 h. The hot solution is filtered and the yellow solid collected. A lower second phase forms in the filtrate as a brown oil, which crystallizes upon cooling to give the crude product. Crystallization from ethyl acetate-pentane gives 2-(3-chlorophenyl)-1-(2,4,6-trihydroxyphenyl)ethanone) as light yellow crystals of mp. 182.6-184.7 °C. ^{1}H-NMR (D_6-DMSO): 12.25 (s), 10.52 (s), 8.49 (s), 7.35-7.19 (m), 5.90 (t), 4.40 (s); MS: m/z = 279 (M^+); Anal. ($C_{14}H_{11}O_4Cl$ (278.75): C 60.34 (found: 61.50), H 3.98 (found 3.27).

Example 2: 3-(3-Chlorophenyl)-5-hydroxy-7-methoxy-isoflavone

0.12 g (0.426 mMol) of 3-(3-chlorophenyl)-5,7-dihydroxy-isoflavone (Example 1) is dissolved in 6 ml of methanol and cooled to -20 °C. 10 ml of an etherial solution of diazomethane is added and the reaction mixture is stirred for 4 days at -14 °C. The solution is evaporated to dryness and the residue dissolved in ethyl acetate-water. The organic phase is washed with water, dried and evaporated. The crude yellow solid is purified by flash chromatography (toluene-ethyl acetate -6:4) to yield 3-(3-Chlorophenyl)-5-hydroxy-7-methoxy-isoflavone. Crystallisation from toluene gives yellowish crystals of m.p. 147.5-150.2 °C. ^{1}H-NMR (D_6-DMSO): 12.76 (s), 8.59 (s), 7.68 (t), 7.56-7.46 (m), 6.70 (d), 6.44 (d), 3.88 (s); MS: m/z = 302 (M^+); Anal. ($C_{16}H_{11}O_4Cl$ (302.71): C 60.34 (found: 61.50), H 3.98 (found 3.27).

3-(3-Chlorophenyl)-5,7-dimethoxy-isoflavone (mp. 107-112 °C) is isolated as a by-product in minor quantities.

In analogy to example 1 or example 2, the following examples 3, 4 and 5a) to 5j) are prepared:

Example 3: 3-(3-Bromophenyl)-5,7-dihydroxy-isoflavone

The compound is prepared from 2-(3-bromophenyl)-1-(2,4,6-trihydroxyphenyl)ethanone (synthesis in analogy to Step 1a) starting from phloroglucine and (instead of 3-chlorobenzylcyanide) 3-bromobenzylcyanide) and boron trifluoride etherate.

Example 4: 3-(3-Bromophenyl)-5-hydroxy-7-methoxy-isoflavone

Synthesis is done in analogy to example 2 from 3-(3-bromophenyl)-5,7-dihydroxy-isoflavone (Example 3) and diazomethane.

Example 5:

a) 3-(3-Chlorophenyl)-5,6,7-trihydroxy-isoflavone

(starting from 1,2,3,5-tetrahydroxybenzene (Chem. Abstr. Service No. 634-94-6) and 3-chlorobenzylcyanide).

b) 3-(3-Bromophenyl)-5,6,7-trihydroxy-isoflavone

(starting from 1,2,3,5-tetrahydroxybenzene (Chem. Abstr. Service No. 634-94-6) and 3-bromobenzylcyanide).

c) 3-(3-Chlorophenyl)-5,6-dihydroxy-7-methoxy-isoflavone

(starting from 1-methoxy-2,3,5-trihydroxybenzene (Beilstein E III, Vol. 8, p 3981) and 3-chlorobenzylcyanide).

d) 3-(3-Bromophenyl)-5,6-dihydroxy-7-methoxy-isoflavone

(starting from 1-methoxy-2,3,5-trihydroxybenzene (Beilstein E III, Vol 8, p 3981) and 3-bromobenzylcyanide).

e) 3-(3-Chlorophenyl)-5-hydroxy-6,7-dimethoxy-isoflavone

(starting from 1,2-dimethoxy-3,5-dihydroxybenzene (Chem. Abstr. Service No. 13077-75-3) and 3-chlorobenzylcyanide).

f) 3-(3-Bromophenyl)-5-hydroxy-6,7-dimethoxy-isoflavone

(starting from 1,2-dimethoxy-3,5-dihydroxybenzene (Chem. Abstr. Service No. 13077-75-3) and 3-bromobenzylcyanide).

g) 3-(3-Chlorophenyl)-5-hydroxy-6,7-methylenedioxy-isoflavone

(starting from 1,2-methylenedioxy-3,5-dihydroxybenzene and 3-chlorobenzlycyanide).

h) 3-(3-Bromophenyl)-5-hydroxy-6,7-methylenedioxy-isoflavone

(starting from 1,2-methylenedioxy-3,5-dihydroxybenzene and 3-bromobenzlycyanide).

i) 3-(3,4-Dichlorophenyl)-5,7-dihydroxy-isoflavone

(starting from phloroglucine and 3,4-dichlorobenzylcyanide (Fluka, Buchs, Switzerland).

j) 3-(3,4-Dichlorophenyl)-5-hydroxy-7-methoxy-isoflavone

(starting from 3-(3,4-dichlorophenyl)-5,7-dihydroxy-isoflavone (synthesis in analogy to Example 3, but starting from phloroglucine and (instead of 3-bromobenzylcyanide) 3,4-dichlorobenzylcyanide) and diazomethane).

Example 6: 3-(3-Chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone

DMF (1 ml) is cooled to 10 °C and 0.74 ml (9.67 mMol) of phosphoroxychloride is added. The reaction mixture is stirred at room temperature for 30 min, developing a deep pink colour. 2.80 g (8.06 mMol) of 2-(3-chlorophenyl)-1-(2,4-dimethoxy-6-acetamide-phenyl)-ethanone, dissolved in 2 ml of DMF, is added to the DMF-$POCl_3$-complex, upon which the colour of the reaction mixture turns into deep red. The mixture is stirred for 1 h at room temperature, then 72 h at 80 °C, and finally poured onto ice. The dark-brown mixture is purified by flash chromatography (toluene/ethyl acetate - 6:4) yielding the crude product. Crystallization from DMF gives fine yellow needles of 3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone of m.p. 268.5-271.6 °C.

^{1}H-NMR (D_6-DMSO): 14.75 (s), 12.40 (s), 8.25 (s), 7.81 (t), 7.66 (dd), 7.46-7.43 (m), 6.46, 6.23 (2d), 3.82 (s); MS: m/z = 301 (M^+). Anal. ($C_{16}H_{12}O_3NCl$ (301.78): C 63.67 (found: 63.41), H 4.02 (found 4.14, N 4.64 (found: 4.72).

Minor quantities of the by-product 3-(3-chlorophenyl)-4-chloro-5,7-dimethoxy-4-quinoline of m.p. 155.5-156.9 °C (crystallization from ethanol) are obtained by working up 24 h at room termperature and purification by flash chromatography.

The starting material is prepared in the following way:

Step 6a): 2-(3-Chlorophenyl)-1-(2,4-dimethoxy-6-acetamide-phenyl)ethanone

0.27 g (1.39 mMol) of acetamido-3,5-dimethoxybenzene (Chem. Abstr. Service No. 98288-51-8; can be obtained also from 1-amino 3,5-dimethoxybenzene (Fluka, Buchs, Switzerland) by acetylation with acetic anhydride/pyridine) is partially dissolved in 50 ml of 1,2-dichloroethane and cooled to 0 °C . 0.33 ml (2.77 mMol) of stannic chloride is added. 0.316 g (1.66 mMol) of 3-chlorophenyl-acetyl chloride (Fluka, Buchs, Switzerland) is added over 15

min at room temperature. After full addition, the solution turns deep yellow-brown. The reaction is stirred at room temperature for 3 h, poured onto ice and extracted with methylene chloride. The organic phase is washed with water, dried and evaporated to dryness to yield a brown oil which is purified by flash chromatography (toluene/ethyl acetate - 6:4) to yield 0.31 g of crude product. Crystallization from toluene gave creamy needles of 2-(3-chlorophenyl)-1-(2,4-dimethoxy-6-acetamide-phenyl)ethanone of mp. 110- 112.5 °C. ^{1}H-NMR ($CDCl_3$): 11.42 (s), 797 (d), 7.27-7.20 (m), 7.07 (dd), 6.18 (d), 4.22 (s), 3.85 (s), 1.26 (s); MS: m/z = 347 (M^+), corresponding to $C_{18}H_{18}O_4NCl$.

In analogy to example 6, the following Examples 7a) to 7e) are prepared:

Example 7:

a) 3-(3-Bromophenyl)-5-hydroxy-7-methoxy-4-quinolone

(starting from 3-bromophenyl-acetylchloride [Chem. Abstr. Service No. 98288-51-8; can also be obtained from 3-bromophenyl-acetic acid (Fluka, Buchs, Switzerland) by reaction with thionyl chloride or phosphortrichloride under reflux] and acetamido-3,5-dimethoxybenzene).

b) 3-(3,4-Dichlorophenyl)-5-hydroxy-7-methoxy-4-quinolone

(starting from 3,4-dichlorophenyl-acetylchloride [can be obtained from 3,4-dichlorophenyl-acetic acid (Aldrich, Buchs, Switzerland) by reaction with thionyl chloride or phosphortrichloride under reflux] and acetamido-3,5-dimethoxybenzene).

c) 3-(3-Hydroxyphenyl)-5-hydroxy-7-methoxy-4-quinolone

(starting from 3-methoxyphenyl-acetylchloride [can be obtained from 3-methoxphenyl-acetic acid (Fluka, Buchs, Switzerland) by reaction with thionyl chloride or phosphortrichloride under reflux] and acetamido-3,5-dimethoxybenzene with 2-(3-methoxyphenyl)-1-(2,4-dimethoxy-6-acetamide-phenyl)ethanone as intermediate, which is then demethylated with the DMF-$POCl_3$-complex under removal of two methoxy groups, yielding the title compound).

d) 3-(3-Chlorophenyl)-5-hydroxy-6,7-dimethoxy-4-quinolone

(starting from acetamido-3,4,5-trimethoxybenzene (Chem. Abstr. Service No. 4304-24-9) and 3-chlorophenyl-acetyl chloride).

e) 3-(3-Chlorophenyl)-5-hydroxy-6,7-methylenedioxy-4-quinolone

(starting from acetamido-3-methoxy-4,5-methylenedioxy-benzene (Chem. Abstr. Service No. 69151-43-5) and 3-chlorophenyl-acetyl chloride).

Example 8: 3-(3-Chlorophenyl)-5,7-dihydroxy-4-quinolone

Boron tribromide (0.02 ml, 1.03 mmol) is added to a suspension of 3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone (Example 6) in toluene (10 ml) and held under reflux for 18 h. The dark brown suspension is cooled to 0 °C, methanol is addes, and then the solvents are removed *in vacuo*. Diethyl ether is added and removed by decantation, leaving a crude brown residue. Purification by flash chromatography (toluene/ethyl acetate 6:4) yields the title compound as a yellow solid, m.p. 145-147 °C, MS: m/z = 287 (M^+), corresponding to $C_{15}H_{10}ONCl$ (287.6); ^{1}H-NMR (D_6-DMSO): 14,70 (s,-HO-C(5)); 12.26 (d,J = 6.4, H-N); 10.32 (s,HO-C(7)); 8.16 (d,J = 6.4, H-C(2)); 7.79 (t,J = 1.8, H-C(2')); 7.66-7.63 (m, H-C(5')); 7.44-7.31 (m,H-C(4'), H-C(6')); 6.35 (d,J = 2.1, (H-C(8)); 6.06 (d,J = 2.1, (H-C(6)).

In analogy to example 8, the following compounds of Example 9 are synthesized:

Example 9:

a) 3-(3-Bromophenyl)-5,7-dihydroxy-4-quinolone

(starting from 3-(3-Bromophenyl)-5-hydroxy-7-methoxy-4-quinolone, Example 7a).

b) 3-(3,4-Dichlorophenyl)-5,7-dihydroxy-4-quinolone

(starting from 3-(3,4-dichlorophenyl)-5-hydroxy-7-methoxy-4-quinolone, Example 7b).

c) 3-(3-Hydroxyphenyl)-5,7-dihydroxy-4-quinolone

(starting from 3-(3-hydroxyphenyl)-5-hydroxy-7-methoxy-quinolone, Example 7c).

d) 3-(3-Chlorophenyl)-5,6,7-trihydroxy-4-quinolone

(starting from 3-(3-chlorophenyl)-5-hydroxy-6,7-dimethoxy-4-quinolone, Example 7d).

Example 10: N-Methyl-3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone

0.123 g (0.41 mMol) of 3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone (Example 6) is dissolved in 4ml of DMF. Then methyl iodide (0.03ml, 0.48 mMol) and potassium carbonate (0.1g, 1 mMol) are added. The reaction mixture is stirred at room temperature for 30 min, poured into water and extracted with ethyl acetate. The organic phase is dried and the solvent removed in vacuo to yield a yellow solid. Crystallization of this solid from toluene gives N-methyl-3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone as fine yellow needles of mp.177.4-183 °C. ^{1}H-NMR (D_6-DMSO): 15.27 (s), 8.39 (s), 7.80 (t), 7.67-7.66 (m), 7.46-7.37 (m), 6.45, 6.33 (2d), 3.88 (s), 3.85 (s); MS: m/z = 315 (M^+), corresponding to $C_{17}H_{14}O_3NCl$.

Example 11: N-(2-Phenylethyl)-3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone

60mg (0.198 mMol) of 3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone (Example 6) is dissolved in 5 ml of DMF. Then 0.1 ml (0.74 mMol) of 2-phenylethyl bromide (Fluka, Buchs, Switzerland) and 0.1 g (1 mMol) of potassium carbonate is added. The reaction mixture is stirred at room temperature for 17 h, poured into water and extracted with ethyl acetate. The organic phase is dried, and solvent is removed in vacuo to yield a yellow oil. Purification by flash chromatography (toluene/ethyl acetate - 9: 1) gives N-(2-phenylethyl)-3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone of m.p. 142.6 - 144.5 °C. (crystallisation from toluene) in the form of yellow needles. ^{1}H-NMR ($CDCl_3$): 15.11 (s), 7.34-7.02 (m), 6.38 (d), 6.31 (d), 4.27 (t), 3.88 (s), 3.14 (t); MS: m/z = 405 (M^+), corresponding to $C_{24}H_{20}O_3NCl$ (405.88).

In an analogous way as described in example 10, if not described otherwise, the following examples 12, 13 and 14a) to 14 l) are prepared:

Example 12: 3-(3-Chlorophenyl)-5-hydroxy-7-methoxy-1-methoxycarbonylmethyl-4-quinolone

The title compound is prepared from 0.1 g (0.332 mMol) of 3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone (example 6) and 0.032 ml (0.332 mMol) of bromoacetic acid methylester (Fluka, Buchs, Switzerland): M.p. 151.4-156.5 °C; MS: m/z = 373 (M^+), corresponding to $C_{19}H_{16}O_5NCl$ (373.85).

Example 13: 3-(3-Chlorophenyl)-1-ethoxycarbonylmethyl-5-hydroxy-7-methoxy-4-quinolone

The title compound is prepared from3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone (Example 6) and bromoacetic acid ethylester (Fluka, Buchs, Switzerland).

Example 14:

a) 1-(Carboxy-methyl)-3-(3-chlorphenyl)-5-hydroxy-7-methoxy-4-quinolone-
(starting from the title compound of Example 12 or 13 by hydrolysis with lithium hydroxide solution).

b) 1-(Aminocarbonyl-methyl)-3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone

(starting material: 3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone (example 6) and bromoacetic acid amide (Fluka, Buchs, Switzerland) in analogy to example 13); The title compound has a m.p. of 268-269 °C.

c) N-Acetyl-3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone

(starting from 3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone (example 6) by reaction with acetic anhydride in pyridine).

d) N-Ethyl-3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone

(starting from 3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone (example 6) by reaction with ethyl iodide in analogy to example 10).

e) N-Propyl-3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone

(starting from 3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone (example 6) by reaction with n-propyl iodide in analogy to example 10).

f) N-Isopropyl-3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone

(starting from 3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone (example 6) by reaction with isopropyl iodide).

g) 1-(Carboxy-methyl)-3-(3-Chlorophenyl)-5,7-dihydroxy-4-quinolone

(starting from 3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone (example 8) and bromoacetic acid methyl ester via 3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone-N-methyl acetate which is hydrolyzed with lithium hydroxide solution).

h) 1-(Aminocarbonyl-methyl)-3-(3-Chlorophenyl)-5,7-dihydroxy-4-quinolone

(starting from 3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone (example 8) and bromoacetic acid amide).

i) N-Acetyl-3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone

(starting from 3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone (example 8) and acetic anhydride in the presence of pyridine).

j) N-Ethyl-3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone

(starting from 3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone (example 8) and ethyl iodide in analogy to example 10).

k) N-Propyl-3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone

(starting from 3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone (example 8) and n-propyl iodide in analogy to example 10).

l) N-Isopropyl-3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone

(starting from 3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone (example 8) and isopropyl iodide in analogy to example 10).

Example 15: Dry-filled capsules

5000 capsules, each comprising as active ingredient 0.25 g of one of the compounds of formula I mentioned in the preceding Examples, are prepared as follows:

Composition	
active ingredient	1250 g
talcum	180 g
wheat starch	120 g
magnesium stearate	80 g
lactose	20 g

Preparation process: The mentioned substances are pulverised and forced through a sieve of 0.6 mm mesh size. 0.33 g portions of the mixture are introduced into gelatin capsules using a capsule-filling machine.

Example 16: Soft capsules

5000 soft gelatin capsules, each comprising as active ingredient 0.05 g of one of the compounds of formula I mentioned in the preceding Examples 1 to 14 l), are prepared as follows:

Composition		
active ingredient	250 g	
Lauroglycol		2 litres

Preparation process: The active ingredient is pulverised and suspended in Lauroglycol® (propylene glycol laurate, Gattefossé S.A., Saint Priest, France) and ground in a wet pulveriser to a particle size of approx. from 1 to 3 μm. 0.419 g portions of the mixture are then introduced into soft gelatin capsules using a capsule-filling machine.

Example 17: Soft capsules

5000 soft gelatin capsules, each comprising as active ingredient 0.05 g of one of the compounds of formula I mentioned in the preceding Examples 1 to 14 l), are prepared as follows:

Composition	
active ingredient	250 g
PEG 400	1 litre
Tween 80	1 litre

Preparation process: The active ingredient is pulverised and suspended in PEG 400 (polyethylene glycol having an M_r of from approx. 380 to approx. 420, Fluka, Switzerland) and Tween®80 (polyoxyethylene sorbitan monolaurate, Atlas Chem. Ind. Inc., USA, supplied by Fluka, Switzerland) and ground in a wet pulveriser to a particle size of approx. from 1 to 3 μm. 0.43 g portions of the mixture are then introduced into soft gelatin capsules using a capsule-filling machine.

Example 18: Inhibition of EGF-R protein tyrosine kinase:

In accordance with the test protocol described above, using the recombinant intracellular domain of the EGF-receptor (EGF-R ICD; see, for example, E. McGlynn *et al.*, Europ. J. Biochem. 207, 265-275 (1992)), the following IC_{50} values (μM) are obtained with the compounds of the respective Examples:

Compound of Example	IC_{50} (μM)
1	0.095
2	1.27
6	0.038
8	0.008
10	0.17
11	4
12	0.064
14b)	0.023

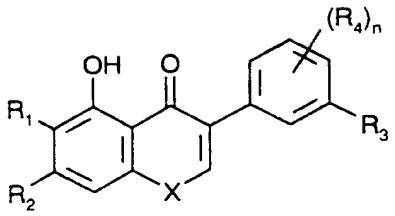
Example 19: Inhibition of the growth of the epidermoid mouse keratinocyte cell line:

In accordance with the test system given above (see Meyer *et al.*, Int. J. Cancer 43, 851 (1989)), the inhibitory activity of the compounds of formula I on the growth of the epidermoid mouse keratinocyte cell line is determined as follows, the result being given as IC_{50} (μM):

Compound of Example	IC_{50} (μM)
1	16.0
2	45.2
6	11.4
8	10.2
10	2.83
11	4.93
12	9.55

What is claimed is

1. The use of a compound of the formula I,



(I)

wherein

R_1 and R_2, independently of each other, represent hydrogen, hydroxy or lower alkoxy, or R_1 and R_2 together form lower alkylenedioxy;

R_3 is halogen, lower alkyl, halogen substituted lower alkyl, hydroxy, phenyloxy, C_3-C_7-cycloalkyloxy or lower alkoxy;

any R_4 is, independently of R_3 and independently of any other R_4 if present, selected from halogen, lower alkyl, halogen substituted lower alkyl, hydroxy, phenyloxy, C_3-C_7-cycloalkyloxy or lower alkoxy;

X is oxygen, imino or (halogen-substituted or unsubstituted lower alkanoyl, [lower alkyl or carboxy-, lower alkoxycarbonyl-, aminocarbonyl-, N-mono- or N,N-di-lower alkylaminocarbonyl]-lower alkyl; or C_6-C_{12}-aryl)-substituted imino; and

n is 0, 1, 3 or 4;

or a salt thereof if at least one salt-forming group is present,

for the preparation of a pharmaceutical composition for the treatment of a proliferative disease that depends on protein kinase activity.

2. The use according to claim 1 of a compound of formula I, or a salt thereof if at least one salt-forming group is present, where the disease to be treated is a disease that depends on protein tyrosine kinase activity.

3. The use according to claim 1 of a compound of formula I, or a salt thereof if at least one salt-forming group is present, where the disease to be treated is a tumour disease and/or an epidermal hyperproliferative disease.

4. The use according to claim 1 of a compound of claim 1, or a salt thereof if at least one salt-forming group is present, where the disease to be treated is a neoplasia of epithelial character, a leukaemia and/or psoriasis.

5. The use according to any one of claims 1 to 4, where a compound of formula I, wherein R_1 and R_2, independently of each other, represent hydrogen; hydroxy; or lower alkoxy; or together form lower alkylenedioxy;

R_3 is halogen or hydroxy;

R_4 is, independently of R_3, halogen;

X is oxygen, imino or imino substituted with lower alkanoyl; lower alkyl; carboxy-lower alkyl; lower-alkoxycarbonyl-lower alkyl; aminocarbonyl; or phenyl-lower alkyl;

and
n is 0 or 1,

or a salt thereof if at least one salt-forming group is present, is used.

6. The use according to any one of claims 1 to 4, where a compound of formula I selected from the group comprising
3-(3-chlorophenyl)-5,7-dihydroxy-isoflavone;
3-(3-chorophenyl)-5-hydroxy-7-methoxy-isoflavone;
3-(3-bromophenyl)-5,7-dihydroxy-isoflavone;
3-(3-bromophenyl-5-hydroxy-7-methoxy-isoflavone;
3-(3-chlorophenyl)-5,6,7-trihydroxy-isoflavone;
3-(3-bromophenyl)-5,6,7-trihydroxy-isoflavone;

3-(3-chlorophenyl)-5,6-dihydroxy-7-methoxy-isoflavone;
3-(3-bromophenyl)-5,6-dihydroxy-7-methoxy-isoflavone;
3-(3-chlorophenyl)-5-hydroxy-6,7-dimethoxy-isoflavone;
3-(3-bromophenyl)-5-hydroxy-6,7-dimethoxy-isoflavone;
3-(3-chlorophenyl)-5-hydroxy-6,7-methylenedioxy-isoflavone;
3-(3-bromophenyl)-5-hydroxy-6,7-methylenedioxy-isoflavone;
3-(3,4-Dichlorophenyl)-5,7-dihydroxy-isoflavone; and
3-(3,4-Dichlorophenyl)-5-hydroxy-7-methoxy-isoflavone;
or a salt thereof, where salt-froming groups are present, is used.

7. A compound of the formula I, wherein
R_1 and R_2, independently of each other, represent hydrogen; hydroxy; or lower alkoxy; or together form lower alkylenedioxy;

R_3 is halogen or hydroxy;

R_4 is, independently of R_3, halogen;

X is oxygen, imino or imino substituted with lower alkanoyl; lower alkyl; carboxy-lower alkyl; lower-alkoxycarbonyl-lower alkyl; aminocarbonyl; or phenyl-lower alkyl;

and
n is 0 or 1,

with the proviso that, (i) when X is oxygen and the other moieties are as defined above, then R_3 is halogen, and (ii) when X is oxygen and R_1 is hydrogen and the other moieties have the meanings given above, then R_2 is lower alkoxy, especially methoxy;

or a salt thereof if at least one salt-forming group is present.

8. A compound of the formula I according to claim 7, wherein
R_1 and R_2, independently of each other, represent hydrogen; hydroxy; or lower alkoxy; or together form lower alkylenedioxy; and lower alkoxy;

R_3 is halogen or hydroxy;

R_4 is, independently of R_3, halogen;

X is imino or imino substituted with lower alkanoyl; lower alkyl; carboxy-lower alkyl; lower-alkoxycarbonyl-lower alkyl; aminocarbonyl (-CO-NH_2); or phenyl-lower alkyl;

and
n is 0 or 1,

or a salt thereof if at least one salt-forming group is present.

9. A compound of the formula I according to claim 7, wherein
R_1 and R_2, independently of each other, represent hydrogen; hydroxy; or lower alkoxy; or together form lower alkylenedioxy;

R_3 is halogen or hydroxy;

R_4 is, independently of R_3, halogen;

X is imino or imino substituted with lower alkyl; lower-alkoxycarbonyl-lower alkyl; aminocarbonyl; or phenyl-lower alkyl;

and
n is 0 or 1, especially 0;

or a salt thereof if at least one salt-forming group is present.

10. A compound of formula I according to claim 7, or a salt thereof where at least one salt-forming group is present, said compound being selected from the group comprising
3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone;
3-(3-bromophenyl)-5-hydroxy-7-methoxy-4-quinolone;

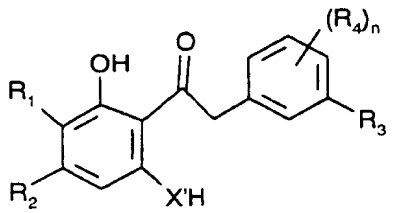
3-(3,4-dichlorophenyl)-5-hydroxy-7-methoxy-4-quinolone;
3-(3-hydroxyphenyl)-5-hydroxy-7-methoxy-4-quinolone;
3-(3-chlorophenyl)-5-hydroxy-6,7-dimethoxy-4-quinolone;
3-(3-chlorophenyl)-5-hydroxy-6,7-methylenedioxy-4-quinolone;
3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone;
3-(3-bromophenyl)-5,7-dihydroxy-4-quinolone;
3-(3,4-dichlorophenyl)-5,7-dihydroxy-4-quinolone;
3-(3-hydroxyphenyl)-5,7-dihydroxy-4-quinolone;
3-(3-chlorophenyl)-5,6,7-trihydroxy-4-quinolone;
N-methyl-3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone;
N-(2-phenylethyl)-3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone;
3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone-N-methylacetate;
3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone-N-ethylacetate;
3-(3-chlorphenyl)-5-hydroxy-7-methoxy-4-quinolone-N-acetic acid;
3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone-N-acetamide;
N-acetyl-3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone;
N-ethyl-3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone;
N-propyl-3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone;
N-isopropyl-3-(3-chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone;
3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone-N-acetic acid;
3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone-N-acetamide;
N-acetyl-3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone;
N-ethyl-3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone;
N-propyl-3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone; and
N-isopropyl-3-(3-chlorophenyl)-5,7-dihydroxy-4-quinolone.

11. A compound of formula I according to claim 7, or a salt thereof where at least one salt-forming group is present, said compound being selected from the group comprising:
3-(3-chorophenyl)-5-hydroxy-7-methoxy-isoflavone;
3-(3-bromophenyl-5-hydroxy-7-methoxy-isoflavone;
3-(3-chlorophenyl)-5,6,7-trihydroxy-isoflavone;
3-(3-bromophenyl)-5,6,7-trihydroxy-isoflavone;
3-(3-chlorophenyl)-5,6-dihydroxy-7-methoxy-isoflavone;

3-(3-bromophenyl)-5,6-dihydroxy-7-methoxy-isoflavone;
3-(3-chlorophenyl)-5-hydroxy-6,7-dimethoxy-isoflavone;
3-(3-bromophenyl)-5-hydroxy-6,7-dimethoxy-isoflavone;
3-(3-chlorophenyl)-5-hydroxy-6,7-methylenedioxy-isoflavone;
3-(3-bromophenyl)-5-hydroxy-6,7-methylenedioxy-isoflavone; and
3-(3,4-dichlorophenyl)-5-hydroxy-7-methoxy-isoflavone.

12. A compound of formula I, or a salt thereof if at least one salt-forming group is present, said compound being selected from the group comprising
3-(3-bromophenyl)-5,7-dihydroxy-isoflavone; and
3-(3,4-dichlorophenyl)-5,7-dihydroxy-isoflavone.

13. A process for the preparation of a compound of formula I according to claim, characterized by reacting a phenylketone of the formula III,.



(III)

wherein R_1, R_2, R_3, R_4 and n have the meanings given above for compounds of formula I and wherein X' is oxygen (-O-) or imino (-NH-), any free functional groups present being protected if necessary by readily removable protecting groups,

with a reactive formaldehyde derivative, and removing any protecting groups that are present,

where a starting material where appropriate and where a salt forming group is present may also be used in the form of a salt;

and, if desired, transforming a compound of formula I into a different compond of formula I, converting a resulting free compound of formula I into a salt, converting a resulting salt of a compound of formula I into the free compound or into a diffe-

rent salt, and/or separating a mixture of isomeric compounds of formulal into the individual isomers.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/05697

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D311/36 C07D215/22 C07D493/04 A61K31/35 A61K31/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
3 February 1998	25/02/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

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